

Nuclear Medicine, Diagnostic Tomography and Imaging:

X-ray, CAT, Scanning, PET, FFT Imaging and Microscopy

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Book's Front Cover



High resolution PET Scanner

Early Medical Diagnostics using Nuclear Medicine

Nuclear medicine

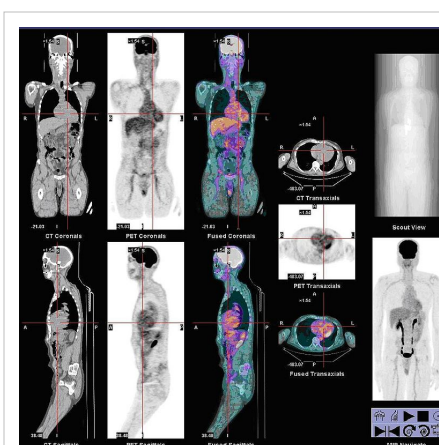
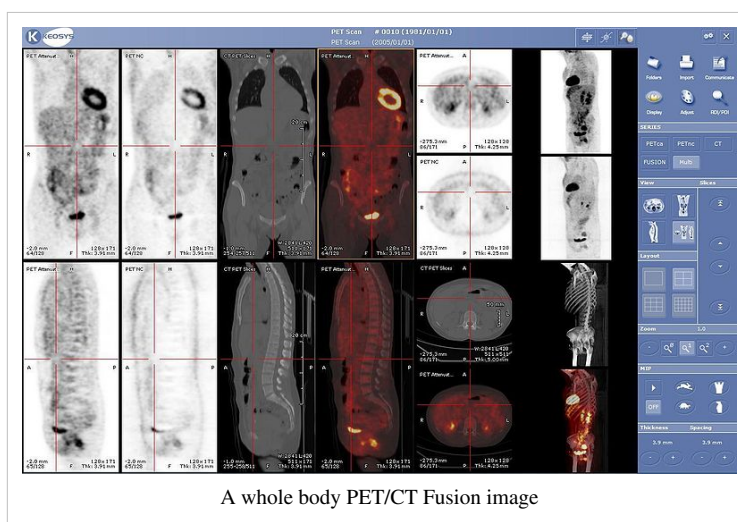
Nuclear medicine is a branch or specialty of medicine and medical imaging that uses radionuclides and relies on the process of radioactive decay in the diagnosis and treatment of disease.

In nuclear medicine procedures, radionuclides are combined with other chemical compounds or pharmaceuticals to form radiopharmaceuticals. These radiopharmaceuticals, once administered to the patient, can localize to specific organs or cellular receptors. This property of radiopharmaceuticals allows nuclear medicine the ability to image the extent of a disease-process in the body, based on the cellular function and physiology, rather than relying on physical changes in the tissue anatomy. In some diseases nuclear medicine studies can identify medical problems at an earlier stage than other diagnostic tests.

Treatment of disease, based on metabolism or uptake or binding of a ligand, may also be accomplished, similar to other areas of pharmacology. However, radiopharmaceuticals rely on the tissue-destructive power of short-range ionizing radiation.

Description of the field

In nuclear medicine imaging, radiopharmaceuticals are taken internally, for example intravenously or orally. Then, external detectors (gamma cameras) capture and form images from the radiation emitted



Normal whole body PET/CT scan with FDG-18. The whole body PET/CT scan is commonly used in the detection, staging and follow-up of various cancers.

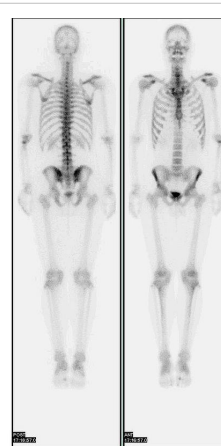
by the radiopharmaceuticals. This process is unlike a diagnostic X-ray where external radiation is passed through the body to form an image.

There are several techniques of diagnostic nuclear medicine. *Scintigraphy* ("scint") is the use of internal radionuclides to create two-dimensional^[1] images. *SPECT* is a 3D tomographic technique that uses gamma camera data from many projections and can be reconstructed in different planes. *Positron emission tomography* (PET) uses coincidence detection to image functional processes.

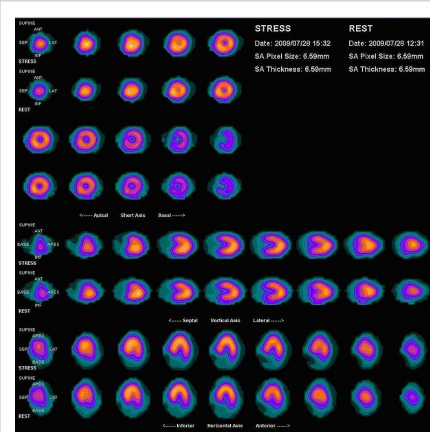
Nuclear medicine tests differ from most other imaging modalities in that diagnostic tests primarily show the physiological function of the system being investigated as opposed to traditional anatomical imaging such as CT or MRI. Nuclear medicine imaging studies are generally more organ or tissue specific (e.g.: lungs scan, heart scan, bone scan, brain scan, etc.) than those in conventional radiology imaging, which focus on a particular section of the body (e.g.: chest X-ray, abdomen/pelvis CT scan, head CT scan, etc.). In addition, there are nuclear medicine studies that allow imaging of the whole body based on certain cellular receptors or functions. Examples are whole body PET scan or PET/CT scans, gallium scans, indium white blood cell scans, MIBG and octreotide scans.

While the ability of nuclear metabolism to image disease processes from differences in metabolism is unsurpassed, it is not unique. Certain techniques such as fMRI image tissues (particularly cerebral tissues) by blood flow, and thus show metabolism. Also, contrast-enhancement techniques in both CT and MRI show regions of tissue which are handling pharmaceuticals differently, due to an inflammatory process.

Diagnostic tests in nuclear medicine exploit the way that the body handles substances differently when there is disease or pathology present. The radionuclide introduced into the body is often chemically bound to a complex that acts characteristically within the body; this is commonly known as a tracer. In the presence of disease, a tracer will often be distributed around the body and/or processed differently. For example, the ligand methylene-diphosphonate (MDP) can be preferentially taken up by bone. By chemically attaching technetium-99m to MDP, radioactivity can be transported and attached to bone via the hydroxyapatite for imaging. Any increased physiological function, such as due to a fracture in the bone, will usually mean increased concentration of the tracer. This often results in the appearance of a 'hot-spot' which is a focal increase in radio-accumulation, or a general increase in radio-accumulation throughout the physiological system. Some disease processes result in the exclusion of a tracer, resulting in the appearance of a 'cold-spot'. Many tracer complexes have been developed to image or treat many different organs, glands, and physiological processes.



A nuclear medicine whole body bone scan. The nuclear medicine whole body bone scan is generally used in evaluations of various bone related pathology, such as for bone pain, stress fracture, nonmalignant bone lesions, bone infections, or the spread of cancer to the bone.



Nuclear Medicine myocardial perfusion scan with Thallium-201 for the rest images (bottom rows) and Tc-Sestamibi for the stress images (top rows). The nuclear medicine myocardial perfusion scan plays a pivotal role in the noninvasive evaluation of coronary artery disease. The study not only identifies patients with coronary artery disease, it also provides overall prognostic information or overall risk of adverse cardiac events for the patient.

Hybrid scanning techniques

In some centers, the nuclear medicine scans can be superimposed, using software or hybrid cameras, on images from modalities such as CT or MRI to highlight the part of the body in which the radiopharmaceutical is concentrated. This practice is often referred to as image fusion or co-registration, for example SPECT/CT and PET/CT. The fusion imaging technique in nuclear medicine provides information about the anatomy and function, which would otherwise be unavailable, or would require a more invasive procedure or surgery.

Practical concerns in nuclear imaging

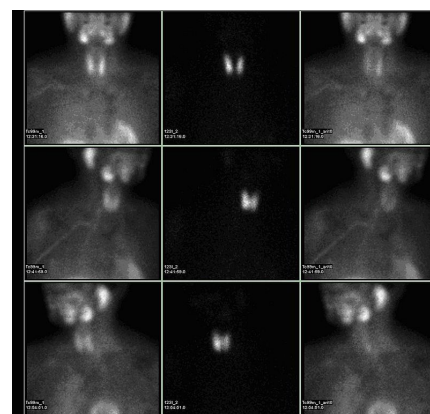
The amount of radiation from diagnostic nuclear medicine procedures is kept within a safe limit and follows the "ALARA" (As Low As Reasonably Achievable) principle. The radiation dose from nuclear medicine imaging varies greatly depending on the type of study. The effective radiation dose can be lower than or comparable to the annual background radiation dose. It can also be in the range or higher than the radiation dose from an abdomen/pelvis CT scan.[2]

Some nuclear medicine procedures require special patient preparation before the study to obtain the most accurate result. Pre-imaging preparations may include dietary preparation or the withholding of certain medications. Patients are encouraged to consult with the nuclear medicine department prior to a scan.

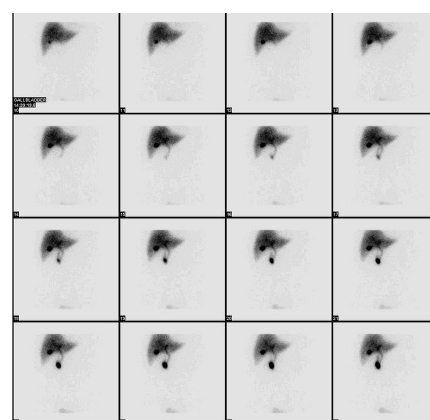
Nuclear medicine therapy

In nuclear medicine therapy, the radiation treatment dose is administered internally (e.g. intravenous or oral routes) rather than from an external radiation source.

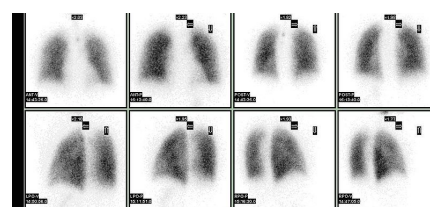
The radiopharmaceuticals used in Nuclear Medicine therapy emit ionizing radiation that travels only a short distance, thereby minimizing unwanted side effects and damage to noninvolved organs or nearby structures. Most Nuclear Medicine therapies can be performed as outpatient procedures since there are few side effects from the treatment and the radiation exposure to the general public can be kept within a safe limit. Common Nuclear Medicine therapies include ^{131}I -sodium iodide for hyperthyroidism and thyroid cancer, Yttrium-90-ibritumomab tiuxetan (Zevalin) and Iodine-131-tositumomab (Bexxar) for refractory Lymphoma, ^{131}I -MIBG (metaiodobenzylguanidine) for neuroendocrine tumors, and palliative bone pain treatment with Samarium-153 or Strontium-89. In some centers the nuclear medicine department may also use implanted capsules of isotopes (brachytherapy) to treat cancer.



A nuclear medicine parathyroid scan demonstrates a parathyroid adenoma adjacent to the left inferior pole of the thyroid gland. The above study was performed with Technetium-Sestamibi (1st column) and Iodine-123 (2nd column) simultaneous imaging and the subtraction technique (3rd column).



Normal hepatobiliary scan (HIDA scan). The nuclear medicine hepatobiliary scan is clinically useful in the detection of the gallbladder disease.

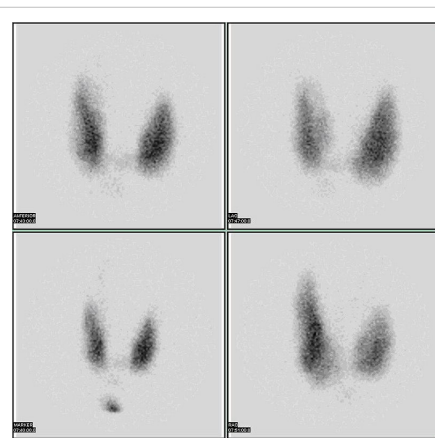


Normal pulmonary ventilation and perfusion (V/Q) scan. The nuclear medicine V/Q scan is useful in the evaluation of pulmonary embolism.

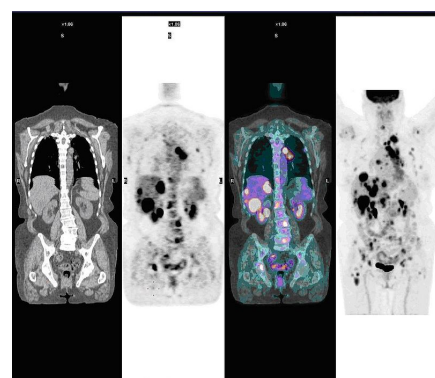
Most nuclear medicine therapies will also require appropriate patient preparation prior to a treatment. Therefore, consultation with the Nuclear Medicine department is recommended prior to therapy.

Molecular medicine

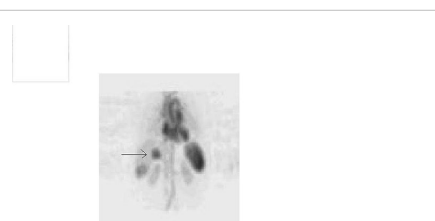
In the future, nuclear medicine may be known as molecular medicine. As our understanding of biological processes in the cells of living organism expands, specific probes can be developed to allow visualization, characterization, and quantification of biologic processes at the cellular and subcellular levels.^[2] Nuclear Medicine is an ideal specialty to adapt to the new discipline of molecular medicine, because of its emphasis on function and its utilization of imaging agents that are specific for a particular disease process.



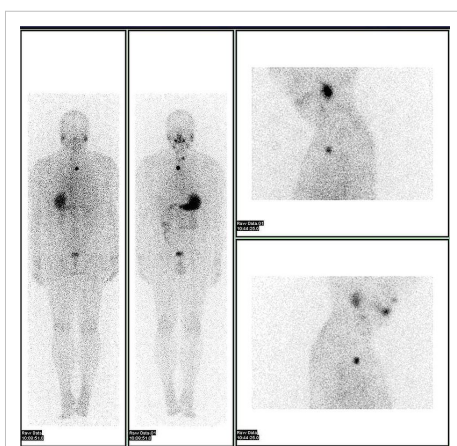
Thyroid scan with Iodine-123 for evaluation of hyperthyroidism.



Abnormal whole body PET/CT scan with multiple metastases from a cancer. The whole body PET/CT scan has become an important tool in the evaluation of cancer.



A nuclear medicine SPECT liver scan with technetium-99m labeled autologous red blood cells. A focus of high uptake (arrow) in the liver is consistent with a hemangioma.



Iodine-123 whole body scan for thyroid cancer evaluation. The study above was performed after the total thyroidectomy and TSH stimulation with thyroid hormone medication withdrawal. The study shows a small residual thyroid tissue in the neck and a mediastinum lesion, consistent with the thyroid cancer metastatic disease. The uptakes in the stomach and bowel are normal physiologic findings.

History

The history of nuclear medicine is rich with contributions from gifted scientists across different disciplines in physics, chemistry, engineering, and medicine. The multidisciplinary nature of Nuclear Medicine makes it difficult for medical historians to determine the birthdate of Nuclear Medicine. This can probably be best placed between the discovery of artificial radioactivity in 1934 and the production of radionuclides by Oak Ridge National Laboratory for medicine related use, in 1946.^[3]

Many historians consider the discovery of artificially produced radionuclides by Frédéric Joliot-Curie and Irène Joliot-Curie in 1934 as the most significant milestone in Nuclear Medicine.^[3] In February 1934, they reported the first artificial production of radioactive material in the *Nature* journal, after discovering radioactivity in aluminum foil that was irradiated with a polonium preparation. Their work built upon earlier discoveries by Wilhelm Konrad Roentgen for X-ray, Henri Becquerel for radioactive uranium salts, and Marie Curie (mother of Irene Curie) for radioactive thorium, polonium and coining the term "radioactivity." Taro Takemi studied the application of nuclear physics to medicine in the 1930s. The history of Nuclear Medicine will not be complete without mentioning these early pioneers.

Nuclear medicine gained public recognition as a potential specialty on December 7, 1946 when an article was published in the *Journal of the American Medical Association* by Sam Seidlin. The article described a successful treatment of a patient with thyroid cancer metastases using radioiodine (I-131). This is considered by many historians as the most important article ever published in Nuclear Medicine.^[4] Although, the earliest use of I-131 was devoted to therapy of thyroid cancer, its use was later expanded to include imaging of the thyroid gland, quantification of the thyroid function, and therapy for hyperthyroidism.

Widespread clinical use of Nuclear Medicine began in the early 1950s, as knowledge expanded about radionuclides, detection of radioactivity, and using certain radionuclides to trace biochemical processes. Pioneering works by Benedict Cassen in developing the first rectilinear scanner and Hal O. Anger's scintillation camera (Anger camera) broadened the young discipline of Nuclear Medicine into a full-fledged medical imaging specialty.

In these years of Nuclear Medicine, the growth was phenomenal. The Society of Nuclear Medicine was formed in 1954 in Spokane, Washington, USA. In 1960, the Society began publication of the Journal of Nuclear Medicine, the premier scientific journal for the discipline in America. There was a flurry of research and development of new radionuclides and radiopharmaceuticals for use with the imaging devices and for in-vitro studies⁵.

Among many radionuclides that were discovered for medical-use, none were as important as the discovery and development of Technetium-99m. It was first discovered in 1937 by C. Perrier and E. Segre as an artificial element to fill space number 43 in the Periodic Table. The development of generator system to produce Technetium-99m in the 1960s became a practical method for medical use. Today, Technetium-99m is the most utilized element in Nuclear Medicine and is employed in a wide variety of Nuclear Medicine imaging studies.

By the 1970s most organs of the body could be visualized using Nuclear Medicine procedures. In 1971, American Medical Association officially recognized nuclear medicine as a medical specialty.^[5] In 1972, the American Board of Nuclear Medicine was established, cementing Nuclear Medicine as a medical specialty.

In the 1980s, radiopharmaceuticals were designed for use in diagnosis of heart disease. The development of single photon emission tomography, around the same time, led to three-dimensional reconstruction of the heart and establishment of the field of Nuclear Cardiology.

More recent developments in Nuclear Medicine include the invention of the first positron emission tomography scanner (PET). The concept of emission and transmission tomography, later developed into single photon emission computed tomography (SPECT), was introduced by David E. Kuhl and Roy Edwards in the late 1950s. Their work led to the design and construction of several tomographic instruments at the University of Pennsylvania. Tomographic imaging techniques were further developed at the Washington University School of Medicine. These innovations led to fusion imaging with SPECT and CT by Bruce Hasegawa from University of California San Francisco (UCSF), and the first PET/CT prototype by D. W. Townsend from University of Pittsburgh in 1998.

PET and PET/CT imaging experienced slower growth in its early years owing to the cost of the modality and the requirement for an on-site or nearby cyclotron. However, an administrative decision to approve medical reimbursement of limited PET and PET/CT applications in oncology has led to phenomenal growth and widespread acceptance over the last few years. PET/CT imaging is now an integral part of oncology for diagnosis, staging and treatment monitoring.

Source of radionuclides, with notes on a few radiopharmaceuticals

About a third of the world's supply, and most of North America's supply, of medical isotopes are produced at the Chalk River Laboratories in Chalk River, Ontario, Canada. (Another third of the world's supply, and most of Europe's supply, are produced at the Petten nuclear reactor in the Netherlands.) The Canadian Nuclear Safety Commission ordered the NRU reactor to be shut down on November 18, 2007 for regularly scheduled maintenance and an upgrade of the safety systems to modern standards. The upgrade took longer than expected and in December 2007 a critical shortage of medical isotopes occurred. The Canadian government unanimously passed emergency legislation, allowing the reactor to re-start on 16 December 2007, and production of medical isotopes to continue.

The Chalk River reactor is used to irradiate materials with neutrons which are produced in great quantity during the fission of U-235. These neutrons change the nucleus of the irradiated material by adding a neutron, or by splitting it in the process of nuclear fission. In a reactor, one of the fission products of uranium is molybdenum-99 which is extracted and shipped to radiopharmaceutical houses all over North America. The Mo-99 radioactively beta decays with a half-life of 2.7 days, turning initially into Tc-99m, which is then extracted (milked) from a "moly cow" (see technetium-99m generator). The Tc-99m then further decays, while inside a patient, releasing a gamma photon which is detected by the gamma camera. It decays to its ground state of Tc-99, which is relatively non-radioactive compared to Tc-99m.

The most commonly used radioisotope in PET F-18, is not produced in any nuclear reactor, but rather in a circular accelerator called a cyclotron. The cyclotron is used to accelerate protons to bombard the stable heavy isotope of oxygen O-18. The O-18 constitutes about 0.20% of ordinary oxygen (mostly O-16), from which it is extracted. The F-18 is then typically used to make FDG (see this link for more information on this process).

Common isotopes used in nuclear medicine

isotope	symbol	Z	T _{1/2}	decay	photons	β
Imaging:						
fluorine-18	¹⁸ F	9	109.77 m	β ⁺	511 (193%)	0.664 (97%)
gallium-67	⁶⁷ Ga	31	3.26 d	ec	93 (39%), 185 (21%), 300 (17%)	-
krypton-81m	^{81m} Kr	36	13.1 s	IT	190 (68%)	-
rubidium-82	⁸² Rb	37	1.27 m	β ⁺	511 (191%)	3.379 (95%)
technetium-99m	^{99m} Tc	43	6.01 h	IT	140 (89%)	-
indium-111	¹¹¹ In	49	2.80 d	ec	171 (90%), 245 (94%)	-
iodine-123	¹²³ I	53	13.3 h	ec	159 (83%)	-
xenon-133	¹³³ Xe	54	5.24 d	β ⁻	81 (31%)	0.364 (99%)
thallium-201	²⁰¹ Tl	81	3.04 d	ec	69–83* (94%), 167 (10%)	-
Therapy:						
yttrium-90	⁹⁰ Y	39	2.67 d	β ⁻	-	2.280 (100%)
iodine-131	¹³¹ I	53	8.02 d	β ⁻	364 (81%)	0.807 (100%)
Z = atomic number, the number of protons; T _{1/2} = half-life; decay = mode of decay photons = principle photon energies in kilo-electron volts, keV, (abundance/decay) β = beta maximum energy in mega-electron volts, MeV, (abundance/decay) β ⁺ = β ⁺ decay; β ⁻ = β ⁻ decay; IT = isomeric transition; ec = electron capture * X-rays from progeny, mercury, Hg						

A typical nuclear medicine study involves administration of a radionuclide into the body by intravenous injection in liquid or aggregate form, ingestion while combined with food, inhalation as a gas or aerosol, or rarely, injection of a radionuclide that has undergone micro-encapsulation. Some studies require the labeling of a patient's own blood cells with a radionuclide (leukocyte scintigraphy and red blood cell scintigraphy). Most diagnostic radionuclides emit gamma rays, while the cell-damaging properties of beta particles are used in therapeutic applications. Refined radionuclides for use in nuclear medicine are derived from fission or fusion processes in nuclear reactors, which produce radionuclides with longer half-lives, or cyclotrons, which produce radionuclides with shorter half-lives, or take advantage of natural decay processes in dedicated generators, i.e. molybdenum/technetium or strontium/rubidium.

The most commonly used intravenous radionuclides are:

- Technetium-99m (technetium-99m)
- Iodine-123 and 131

- Thallium-201
- Gallium-67
- Fluorine-18 Fluorodeoxyglucose
- Indium-111 Labeled Leukocytes

The most commonly used gaseous/aerosol radionuclides are:

- Xenon-133
- Krypton-81m
- Technetium-99m Technegas^[6]
- Technetium-99m DTPA

Analysis

The end result of the nuclear medicine imaging process is a "dataset" comprising one or more images. In multi-image datasets the array of images may represent a time sequence (i.e. cine or movie) often called a "dynamic" dataset, a cardiac gated time sequence, or a spatial sequence where the gamma-camera is moved relative to the patient. SPECT (single photon emission computed tomography) is the process by which images acquired from a rotating gamma-camera are reconstructed to produce an image of a "slice" through the patient at a particular position. A collection of parallel slices form a slice-stack, a three-dimensional representation of the distribution of radionuclide in the patient.

The nuclear medicine computer may require millions of lines of source code to provide quantitative analysis packages for each of the specific imaging techniques available in nuclear medicine.

Time sequences can be further analysed using kinetic models such as multi-compartment models or a Patlak plot.

Radiation dose

A patient undergoing a nuclear medicine procedure will receive a radiation dose. Under present international guidelines it is assumed that any radiation dose, however small, presents a risk. The radiation doses delivered to a patient in a nuclear medicine investigation present a very small risk of inducing cancer. In this respect it is similar to the risk from X-ray investigations except that the dose is delivered internally rather than from an external source such as an X-ray machine.

The radiation dose from a nuclear medicine investigation is expressed as an effective dose with units of sieverts (usually given in millisieverts, mSv). The effective dose resulting from an investigation is influenced by the amount of radioactivity administered in megabecquerels (MBq), the physical properties of the radiopharmaceutical used, its distribution in the body and its rate of clearance from the body.

Effective doses can range from 6 μ Sv (0.006 mSv) for a 3 MBq chromium-51 EDTA measurement of glomerular filtration rate to 37 mSv for a 150 MBq thallium-201 non-specific tumour imaging procedure. The common bone scan with 600 MBq of technetium-99m-MDP has an effective dose of approximately 3.5 mSv (1).

Formerly, units of measurement were the curie (Ci), being 3.7×10^{10} Bq, and also 1.0 grams of Radium (Ra-226); the rad (radiation absorbed dose), now replaced by the gray; and the rem (Röntgen equivalent man), now replaced with the sievert. The rad and rem are essentially equivalent for almost all nuclear medicine procedures, and only alpha radiation will produce a higher Rem or Sv value, due to its much higher Relative Biological Effectiveness (RBE). Alpha emitters are nowadays rarely used in nuclear medicine, but were used extensively before the advent of nuclear reactor and accelerator produced radionuclides. The concepts involved in radiation exposure to humans is covered by the field of Health Physics.

Nuclear Medicine Careers

Nuclear Medicine Technologist

The information below is adapted from the Society of Nuclear Medicine (SNM) website on a scientist career. For more information and educational requirements, please see training ^[7]

The nuclear medicine scientist works closely with the nuclear medicine physician. Some of the scientist's primary responsibilities are to:

- Prepare and administer radioactive chemical compounds, known as radiopharmaceuticals
- Perform patient imaging procedures using sophisticated radiation-detecting instrumentation
- Accomplish computer processing and image enhancement
- Analyze biologic specimens in the laboratory
- Provide images, data analysis, and patient information to the physician for diagnostic interpretation.

During an imaging procedure, the scientist works directly with the patient. The scientist:

- Gains the patient's confidence by obtaining pertinent history, describing the procedure and answering any questions
- Monitors the patient's physical condition during the course of the procedure
- Notes any specific patient's comments which might indicate the need for additional images or might be useful to the physician in interpreting the results of the procedure.

Nuclear medicine scientists work in a wide variety of clinical settings, such as

- Community hospitals
- University-affiliated teaching hospitals and medical centers
- Outpatient imaging facilities
- Public health institutions
- Government and private research institutes.

The physician career in nuclear medicine

Nuclear medicine physicians are primarily responsible for interpretation of diagnostic nuclear medicine scans and treatment of certain diseases, such as cancer, thyroid disease and palliative bone pain.

There are a variety of reasons why physicians have chosen to specialize in nuclear medicine. Some became nuclear medicine physicians because of their interest in nuclear physics and medical imaging. Others may have switched to nuclear medicine after training in other specialties, because of the regular work hours (on average about 8 to 10 hours a day). Others have chosen nuclear medicine because of research opportunities in molecular medicine or molecular imaging.

Nuclear medicine physicians frequently interact with other specialties in medicine and consult on a variety of clinical cases. A nuclear medicine report may save a patient from more invasive or high risk procedures, and/or lead to early disease diagnosis. Nuclear Medicine physicians can be called upon to consult on complex or equivocal clinical cases. Aside from consultations with other physicians, nuclear physicians may directly interact with patients through various nuclear medicine therapies (e.g.: I131 thyroid therapy, refractory lymphoma treatment, palliative bone pain therapy).

A disadvantage of a nuclear medicine career for a physician is that it suffers from low job turnover and a small job market, owing to the specialized nature of the field. Advantages of the field include job satisfaction and more regular hours than many fields of medicine, since very rarely are the procedures in this field performed on an emergency basis.

Nuclear medicine residency/training (physicians)

The information below is adapted from the American Board of Nuclear Medicine (ABNM). For more information, please see ABNM^[8]

General professional education requirement in the United States of America: graduation from a medical school approved by the Liaison Committee on Medical Education or the American Association of Colleges of Osteopathic Medicine.

In USA the post-doctoral training in nuclear medicine can be approached from three different pathways:

1. If the person has successfully completed an accredited radiology residency then additional ONE year of training in Nuclear Medicine is required to be eligible for ABNM board certification.
2. If the person has successfully completed a clinical residency (e.g. Internal Medicine, Family Medicine, Surgery, Neurology, etc.) then an additional TWO years of training in Nuclear Medicine is required to be eligible for ABNM board certification.
3. If the person has successfully completed one year of preparatory post-doctoral training (internship) then an additional THREE years of training in Nuclear Medicine is required to be eligible for ABNM board certification.

See also

- Background radiation
- Human experimentation in the United States
- Radiology

Notes

- [1] thefreedictionary.com > scintigraphy (<http://medical-dictionary.thefreedictionary.com/scintigraphy>) Citing: Dorland's Medical Dictionary for Health Consumers, 2007 by Saunders; Saunders Comprehensive Veterinary Dictionary, 3 ed. 2007; McGraw-Hill Concise Dictionary of Modern Medicine, 2002 by The McGraw-Hill Companies
- [2] [www.molecularimagingcenter.org], Gambhir S. Just what is molecular medicine.
- [3] Edwards CI: Tumor localizing radionuclides in retrospect and prospect. *Semin Nucl Med* 3:186–189, 1979.
- [4] Henkin R. et al: Nuclear Medicine. First edition 1996. ISBN 9780801677014.
- [5] <http://interactive.snm.org/docs/whatisnucmed.pdf> from the Society of Nuclear Medicine.
- [6] <http://jcsmr.anu.edu.au/technegas/home.html>
- [7] Training (<http://interactive.snm.org/index.cfm?PageID=985&RPID=193>)
- [8] Acgme (http://www.acgme.org/acWebsite/navPages/nav_200.asp)

Further reading

- Mas JC: A Patient's Guide to Nuclear Medicine Procedures: English-Spanish. Society of Nuclear Medicine, 2008. ISBN 978-0972647892
- Taylor A, Schuster DM, Naomi Alazraki N: A Clinicians' Guide to Nuclear Medicine, 2nd edition. Society of Nuclear Medicine, 2000. ISBN 978-0932004727
- Mark J. Shumate MJ, Kooby DA, Alazraki NP: A Clinician's Guide to Nuclear Oncology: Practical Molecular Imaging and Radionuclide Therapies. Society of Nuclear Medicine, January 2007. ISBN 978-0972647885
- Ell P, Gambhir S: Nuclear Medicine in Clinical Diagnosis and Treatment. Churchill Livingstone, 2004. (1950 pages) ISBN 978-0443073120

External links

- Society of Nuclear Medicine (<http://www.snm.org/>)
- Brochure: What is Nuclear Medicine? (<http://interactive.snm.org/docs/whatisnucmed.pdf>)
- Resource center: information about nuclear medicine (<http://interactive.snm.org/index.cfm?PageID=6309&RPID=1089>)
- International Atomic Energy Agency (IAEA), Division of Human Health, Nuclear Medicine (<http://www-naweb.iaea.org/nahu/nm/default.asp>)
- RADAR Medical Procedure Radiation Dose Calculator and Consent Language Generator (<http://www.doseinfo-radar.com/RADARDoseRiskCalc.html>)
- Association of Image Producers and Equipment Suppliers (<http://www.aipes-eeig.org/>)

Radiobiology

Radiobiology (or *radiation biology*) is the interdisciplinary field of science that studies the biological effects of ionizing and non-ionizing radiation of the whole electromagnetic spectrum, including radioactivity (alpha, beta and gamma), x-rays, ultraviolet radiation, visible light, microwaves, radio wave, low-frequency radiation (such as used in alternate electric transmission, ultrasound thermal radiation (heat), and related modalities. It is a subset of biophysics.

Areas of interest

The interactions between electromagnetic fields (EMF) and organisms can be studied at several levels:

- radiation physics
- radiation chemistry
- molecular and cell biology
- molecular genetics
- cell death and apoptosis
- dose modifying agents
- protection and repair mechanisms
- tissue responses to radiation
- radio-adaptation of living organisms
- high and low-level electromagnetic radiation and health
- specific absorption rates of organisms
- radiation poisoning
- radiation oncology (radiation therapy in cancer)

Radiobiology of non-ionizing radiation includes:

- Bioelectromagnetics
 - Magnetobiology
-

Radiation sources for radiobiology

Radiobiology experiments typically make use of a radiation source which could be:

- An isotopic source, typically ^{137}Cs or ^{60}Co .
- A particle accelerator generating high energy protons, electrons or charged ions. Biological samples can be irradiated using either a broad, uniform beam^[1] or using a microbeam, focused down to cellular or subcellular sizes.
- A UV lamp.

See also

- Radiosensitivity
- Radiology
- Nuclear medicine
- Radioactivity in biology
- Radiophobia
- Cell survival curve
- Relative biological effectiveness
- Health threat from cosmic rays
- Background radiation

Notes

- [1] Pattison, J. E., Hugtenburg, R. P., Beddoe, A. H. and Charles, M. W. (2001), Experimental Simulation of A-bomb Gamma-ray Spectra for Radiobiology Studies, *Radiation Protection Dosimetry* **95**(2):125-136.

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- The Institute for Radiation Biology at the Helmholtz-Center for Environmental Health (<http://www.helmholtz-muenchen.de/en/isb/isb-home/index.html>)

External links

- The Institute for Radiation Biology at the Helmholtz-Center for Environmental Health (<http://www.helmholtz-muenchen.de/en/isb/isb-home/index.html>)
-

Radiopharmacology

Radiopharmacology is the study and preparation of **radiopharmaceuticals**, which are radioactive pharmaceuticals. Radiopharmaceuticals are used in the field of nuclear medicine as tracers in the diagnosis and treatment of many diseases. Many radiopharmaceuticals use technetium-99m (Tc-99m) which has many useful properties as a gamma-emitting tracer nuclide. In the book **Technetium** a total of 31 different radiopharmaceuticals based on Tc-99m are listed for imaging and functional studies of the brain, myocardium, thyroid, lungs, liver, gallbladder, kidneys, skeleton, blood and tumors.^[1]

The term **radioisotope** has historically been used to refer to all radiopharmaceuticals, and this usage remains common. Technically, however, many radiopharmaceuticals incorporate a radioactive tracer atom into a larger pharmaceutically-active molecule, which is localized in the body, after which the radionuclide tracer atom allows it to be easily detected with a gamma camera or similar gamma imaging device. An example is fludeoxyglucose in which fluorine-18 is incorporated into deoxyglucose. Some radioisotopes (for example gallium-67, gallium-68, and radioiodine) are used directly as soluble ionic salts, without further modification. This use relies on the chemical and biological properties of the radioisotope itself, to localize it within the body.

History

See nuclear medicine.

Production

Production of a radiopharmaceutical involves two processes:

- The production of the radionuclide on which the pharmaceutical is based.
- The preparation and packaging of the complete radiopharmaceutical.

Radionuclides used in radiopharmaceuticals are mostly radioactive isotopes of elements with atomic numbers less than that of bismuth, that is, they are radioactive isotopes of elements that also have one or more stable isotopes. These may be roughly divided into two classes:

- Those with fewer neutrons in the nucleus to those required for stability are known as **neutron-deficient**, and tend to be most easily produced using a proton accelerator such as a medical cyclotron.
- Those with excess neutrons in the nucleus to those required for stability are known as **proton-deficient**, and tend to be most easily produced in a nuclear reactor.

Practical use

Because radiopharmaceuticals require special licenses and handling techniques, they are often kept in local centers for medical radioisotope storage, often known as radiopharmacies. A radiopharmacist may dispense them from there, to local centers where they are handled at the nuclear medicine facility.

Specific radiopharmaceuticals

A list of **nuclear medicine radiopharmaceuticals** follows. Some radioisotopes* are used in ionic or inert form without attachment to a pharmaceutical, these are also included. There is a section for each radioisotope with a table of radiopharmaceuticals using that radioisotope. The sections are ordered alphabetically by the English name of the radioisotope. Sections for the same element are then ordered by atomic mass number.

Calcium-47

^{47}Ca is a beta and gamma emitter.

Name	Investigation	Route of administration	<i>In-vitro / in-vivo</i>	Imaging / non-imaging
Ca-47-Ca ²⁺	Bone metabolism	IV	<i>In-vitro</i>	Non-imaging

Carbon-11

^{11}C is a positron emitter.

Name	Investigation	Route of administration	<i>In-vitro / in-vivo</i>	Imaging / non-imaging
C11-L-methyl-methionine	Brain tumour imaging Parathyroid imaging	IV	<i>In-vivo</i>	Imaging

Carbon-14

^{14}C is a beta emitter.

Name	Investigation	Route of administration	<i>In-vitro / in-vivo</i>	Imaging / non-imaging
C14-Glycocholic acid	Breath test for small intestine bacterial overgrowth	Oral	<i>In-vitro</i>	Non-imaging
C14-PABA (para-amino benzoic acid)	Pancreatic studies	Oral	<i>In-vitro</i>	Non-imaging
C14-Urea	Breath test to detect <i>Helicobacter pylori</i>	Oral	<i>In-vitro</i>	Non-imaging
C14-d-xylose	Breath test for small intestine bacterial overgrowth	Oral	<i>In-vitro</i>	Non-imaging

Chromium-51

^{51}Cr is a gamma emitter.

Name	Investigation	Route of administration	<i>In-vitro / in-vivo</i>	Imaging / non-imaging
Cr51-Red blood cells	Red cell volume; sites of sequestration; gastrointestinal blood loss	IV	<i>In-vitro</i>	Non-imaging
Cr51-Cr ³⁺	Gastrointestinal protein loss	IV	<i>In-vitro</i>	Non-imaging
Cr51-EDTA (ethylenediaminetetraacetic acid)	Glomerular filtration rate measurement	IV	<i>In-vitro</i>	Non-imaging

Cobalt-57

^{57}Co is a gamma emitter.

Name	Investigation	Route of administration	<i>In-vitro / in-vivo</i>	Imaging / non-imaging
Co57-Cyanocobalamin (vitamin B ₁₂)	Gastrointestinal absorption	Oral	<i>In-vitro</i>	Non-imaging

Cobalt-58

^{58}Co is a gamma emitter.

Name	Investigation	Route of administration	<i>In-vitro / in-vivo</i>	Imaging / non-imaging
Co58-Cyanocobalamin (vitamin B ₁₂)	Gastrointestinal absorption	Oral	<i>In-vitro</i>	Non-imaging

Erbium-169

^{169}Er is a beta emitter.

Name	Treatment of	Route of administration
Er169-Colloid	Arthritic conditions	Intra-articular

Fluorine-18

^{18}F is a positron emitter with a half life of 109 minutes. It is produced in medical cyclotrons, usually from oxygen-18, and then chemically attached to a pharmaceutical. See PET scan.

Name	Investigation	Route of administration	<i>In-vitro / in-vivo</i>	Imaging / non-imaging
F18-FDG (Fluorodeoxyglucose)	Tumor imaging Myocardial imaging	IV	<i>In-vivo</i>	Imaging
F18-Fluoride	Bone imaging	IV	<i>In-vivo</i>	Imaging
F18-Fluorocholine	Prostate tumor imaging	IV	<i>In-vivo</i>	Imaging

Gallium-67

^{67}Ga is a gamma emitter. See gallium scan.

Name	Investigation	Route of administration	<i>In-vitro / in-vivo</i>	Imaging / non-imaging
Ga67-Ga ³⁺	Tumor imaging	IV	<i>In-vivo</i>	Imaging
Ga67-Ga ³⁺	Infection/inflammation imaging	IV	<i>In-vivo</i>	Imaging

Gallium-68

⁶⁸Ga is a positron emitter, with a 68 minute half life, produced by elution from germanium-68 in a gallium-68 generator. See also positron emission tomography.

Name	Investigation	Route of administration	<i>In-vitro / in-vivo</i>	Imaging / non-imaging
Ga68-Dotatoc or Dotatate	Neuroendocrine tumor imaging	IV	<i>In-vivo</i>	Imaging

Hydrogen-3

³H or tritium is a beta emitter.

Name	Investigation	Route of administration	<i>In-vitro / in-vivo</i>	Imaging / non-imaging
H3-water	Total body water	Oral or IV	<i>In-vitro</i>	Non-imaging

Indium-111

¹¹¹In is a gamma emitter.

Name	Investigation	Route of administration	<i>In-vitro / in-vivo</i>	Imaging / non-imaging
In111-DTPA (diethylenetriaminepenta-acetic acid)	GI transit	Oral	<i>In-vivo</i>	Imaging
In111-DTPA (diethylenetriaminepenta-acetic acid)	Cisternography	Intra-cisternal	<i>In-vivo</i>	Imaging
In111-Leukocytes	Infection/inflammation imaging	IV	<i>In-vivo</i>	Imaging
In111-Platelets	Thrombus imaging	IV	<i>In-vivo</i>	Imaging
In111-Pentetreotide	Somatostatin receptor imaging	IV	<i>In-vivo</i>	Imaging
In111-Octreotide	Somatostatin receptor imaging (Octreoscan)	IV	<i>In-vivo</i>	Imaging

Iodine-123

¹²³I is a gamma emitter. It is used only diagnostically, as its radiation is penetrating and short-lived.

Name	Investigation	Route of administration	<i>In-vitro / in-vivo</i>	Imaging / non-imaging
I123-Iodide	Thyroid uptake	Oral or IV	<i>In-vivo</i>	Non-imaging
I123-Iodide	Thyroid imaging Thyroid metastases imaging	Oral or IV	<i>In-vivo</i>	Imaging
I123-o-Iodohippurate	Renal imaging	IV	<i>In-vivo</i>	Imaging
I123-MIBG (m-iodobenzylguanidine)	Neuroectodermal tumour imaging	IV	<i>In-vivo</i>	Imaging
I123-FP-CIT	SPECT imaging of Parkinson's Disease	IV	<i>In-vivo</i>	Imaging

Iodine-125

¹²³I is a gamma emitter with a long half-life of 59.4 days (the longest of all radioiodines used in medicine). Iodine-123 is preferred for imaging, so I-125 is used diagnostically only when the test requires a longer period to prepare the radiopharmaceutical and trace it, such as a fibrinogen scan to diagnose clotting. I-125's gamma radiation is of medium penetration, making it more useful as a therapeutic isotope for brachytherapy implant of radioisotope capsules for local treatment of cancers.

Name	Investigation	Route of administration	<i>In-vitro / in-vivo</i>	Imaging / non-imaging
I125-fibrinogen	Clot imaging	IV	<i>In-vivo</i>	Imaging

Iodine-131

¹³¹I is a beta and gamma emitter. It is used both to destroy thyroid and thyroid cancer tissues (via beta radiation, which is short-range), and also other neuroendocrine tissues when used in MIBG. It can also be seen by a gamma camera, and can serve as a diagnostic imaging tracer, when treatment is also being attempted at the same time. However iodine-123 is usually preferred when **only** imaging is desired.

Diagnostic

Name	Investigation	Route of administration	<i>In-vitro / in-vivo</i>	Imaging / non-imaging
I131-Iodide	Thyroid uptake	Oral	<i>In-vivo</i>	Non-imaging
I131-Iodide	Thyroid metastases imaging	Oral or IV	<i>In-vivo</i>	Imaging
I131-MIBG (m-iodobenzylguanidine)	Neuroectodermal tumor imaging	IV	<i>In-vivo</i>	Imaging

Therapeutic

Name	Treatment of	Route of administration
I131-Iodide	Thyrotoxicosis	IV or Oral
I131-Iodide	Non-toxic goiter	IV or Oral
I131-Iodide	Thyroid carcinoma	IV or Oral
I131-MIBG (m-iodobenzylguanidine)	Malignant disease	IV

Iron-59

^{59}Fe is a beta and gamma emitter.

Name	Investigation	Route of administration	<i>In-vitro / in-vivo</i>	Imaging / non-imaging
Fe59- Fe^{2+} or Fe^{3+}	Iron metabolism	IV	<i>In-vitro</i>	Non-imaging

Krypton-81m

$^{81\text{m}}\text{Kr}$ is a gamma emitter.

Name	Investigation	Route of administration	<i>In-vitro / in-vivo</i>	Imaging / non-imaging
Kr81m-Gas	Lung ventilation imaging	Inhalation	<i>In-vivo</i>	Imaging
Kr-81m-Aqueous solution	Lung perfusion imaging	IV	<i>In-vivo</i>	Imaging

Nitrogen-13

^{13}N is a positron emitter.

Name	Investigation	Route of administration	<i>In-vitro / in-vivo</i>	Imaging / non-imaging
N13-Ammonia	Myocardial blood flow imaging	IV	<i>In-vivo</i>	Imaging

Oxygen-15

^{15}O is a positron emitter.

Name	Investigation	Route of administration	<i>In-vitro / in-vivo</i>	Imaging / non-imaging
O15-Water	Cerebral blood flow imaging Myocardial blood flow imaging	IV bolus	<i>In-vivo</i>	Imaging

Phosphorus-32

^{32}P is a beta emitter.

Name	Treatment of	Route of administration
P32-Phosphate	Polycythemia and related disorders	IV or Oral

Samarium-153

^{153}Sm is a beta and gamma emitter.

Name	Treatment of	Route of administration
Sm153-EDTMP (Ethylenediaminetetramethylenephosphoric acid)	Bone metastases	IV

Selenium-75

^{75}Se is a gamma emitter.

Name	Investigation	Route of administration	<i>In-vitro / in-vivo</i>	Imaging / non-imaging
Se75-Selenorcholesterol	Adrenal gland imaging	IV	<i>In-vivo</i>	Imaging
Se75-SeHCAT (23-Seleno-25-homo-tauro-cholate)	Bile salt absorption	Oral	<i>In-vivo</i>	Imaging

Sodium-22

^{22}Na is a positron and gamma emitter.

Name	Investigation	Route of administration	<i>In-vitro / in-vivo</i>	Imaging / non-imaging
Na22- Na^+	Electrolyte studies	Oral or IV	<i>In-vitro</i>	Non-imaging

Sodium-24

^{24}Na is a beta and gamma emitter.

Name	Investigation	Route of administration	<i>In-vitro / in-vivo</i>	Imaging / non-imaging
Na24- Na^+	Electrolyte studies	Oral or IV	<i>In-vitro</i>	Non-imaging

Strontium-89

^{89}Sr is a beta emitter.

Name	Treatment of	Route of administration
Sr89-Chloride	Bone metastases	IV

Technetium-99m

$^{99\text{m}}\text{Tc}$ is a gamma emitter. It is obtained on-site at the imaging center as the soluble pertechnetate which is eluted from a technetium-99m generator, and then either used directly as this soluble salt, or else used to synthesize a number of technetium-99m-based radiopharmaceuticals.

Name	Investigation	Route of administration	<i>In-vitro</i> / <i>in-vivo</i>	Imaging / non-imaging
Tc99m-pertechnetate	Thyroid uptake and thyroid imaging Stomach and salivary gland imaging Meckel's diverticulum imaging Brain imaging Micturating cystogram First pass blood flow imaging First pass peripheral vascular imaging	IV	<i>In-vivo</i>	Imaging
Tc99m-pertechnetate	Lacrimal imaging	Eye drops	<i>In-vivo</i>	Imaging
Tc99m-Human albumin	Cardiac blood pool imaging	IV	<i>In-vivo</i>	Imaging
Tc99m-Human albumin	Peripheral vascular imaging	IV	<i>In-vivo</i>	Imaging
Tc99m-Human albumin macroaggregates or microspheres	Lung perfusion imaging	IV	<i>In-vivo</i>	Imaging
Tc99m-Human albumin macroaggregates or microspheres	Lung perfusion imaging with venography	IV	<i>In-vivo</i>	Imaging
Tc99m-Phosphonates and phosphates	Bone imaging	IV	<i>In-vivo</i>	Imaging
Tc99m-Phosphonates and phosphates	Myocardial imaging	IV	<i>In-vivo</i>	Imaging
Tc99m-DTPA (diethylenetriaminepenta-acetic acid)	Renal imaging First pass blood flow studies Brain imaging	IV	<i>In-vivo</i>	Imaging
Tc99m-DTPA (diethylenetriaminepenta-acetic acid)	Lung ventilation imaging	Aerosol inhalation	<i>In-vivo</i>	Imaging
Tc99m-DMSA(V) (dimercaptosuccinic acid)	Tumor imaging	IV	<i>In-vivo</i>	Imaging
Tc99m-DMSA(III) (dimercaptosuccinic acid)	Renal imaging	IV	<i>In-vivo</i>	Imaging
Tc99m-Colloid	Bone marrow imaging GI Bleeding	IV	<i>In-vivo</i>	Imaging
Tc99m-Colloid	Lymph node imaging	Interstitial	<i>In-vivo</i>	Imaging

Tc99m-Colloid	Esophageal transit and reflux imaging	Oral	<i>In-vivo</i>	Imaging
Tc99m-Colloid	Lacrima imaging	Eye drops	<i>In-vivo</i>	Imaging
Tc99m-HIDA (Hepatic iminodiacetic acid)	Functional biliary system imaging	IV	<i>In-vivo</i>	Imaging
Tc99m-Denatured red blood cells	Red cell volume	IV	<i>In-vitro</i>	Non-imaging
Tc99m-Red blood cells	GI bleeding Cardiac blood pool imaging Peripheral vascular imaging	IV	<i>In-vivo</i>	Imaging
Tc99m-MAG3 (mercaptoacetyl triglycine)	Renal imaging First pass blood flow imaging	IV	<i>In-vivo</i>	Imaging
Tc99m-Exametazime	Cerebral blood flow imaging	IV	<i>In-vivo</i>	Imaging
Tc99m-Exametazime labelled leucocytes	Infection/inflammation imaging	IV	<i>In-vivo</i>	Imaging
Tc99m-Sestamibi (MIBI - methoxy isobutyl isonitrile)	Parathyroid imaging Non-specific tumor imaging Thyroid tumor imaging Breast imaging Myocardial imaging	IV	<i>In-vivo</i>	Imaging
Tc99m-Sulesomab (IMMU-MN3 murine Fab'-SH antigranulocyte monoclonal antibody fragments)	Infection/inflammation imaging	IV	<i>In-vivo</i>	Imaging
Tc99m-Technegas	Lung ventilation imaging	Inhalation	<i>In-vivo</i>	Imaging
Tc99m-Human immunoglobulin	Infection/inflammation imaging	IV	<i>In-vivo</i>	Imaging
Tc99m-Tetrofosmin	Parathyroid imaging Myocardial imaging	IV	<i>In-vivo</i>	Imaging
Tc99m-ECD (ethyl cysteinate dimer)	Brain imaging	IV	<i>In-vivo</i>	Imaging

Thallium-201

^{201}Tl is a gamma emitter.

Name	Investigation	Route of administration	<i>In-vitro</i> / <i>in-vivo</i>	Imaging / non-imaging
Tl201-Tl ⁺	Non-specific tumor imaging Thyroid tumor imaging Myocardial imaging Parathyroid imaging	IV	<i>In-vivo</i>	Imaging

Xenon-133

^{133}Xe is a gamma emitter.

Name	Investigation	Route of administration	<i>In-vitro</i> / <i>in-vivo</i>	Imaging / non-imaging
Xe133-gas	Lung ventilation studies	Inhalation	<i>In-vivo</i>	Imaging
Xe133 in isotonic sodium chloride solution	Cerebral blood flow	IV	<i>In-vivo</i>	Imaging

Yttrium-90

^{90}Y is a beta emitter.

Name	Treatment of	Route of administration
Y90-Silicate	Arthritic conditions	Intra-articular
Y90-Silicate	Malignant disease	Intracavitary

See also

Radioactive tracer

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Medical diagnosis

Medical diagnosis refers both to the process of attempting to determine the identity of a possible disease or disorder and to the opinion reached by this process.

The term *diagnostic criteria* designates the combination of signs, symptoms, and test results that the clinician uses to attempt to determine the correct diagnosis. The plural of diagnosis is *diagnoses*, the verb is *to diagnose*, and a person who diagnoses is called a *diagnostician*. The word *diagnosis* (English pronunciation: /daɪ.əɡˈnoʊsɪs/) is derived through Latin from the Greek word διάγνῶσκειν, meaning to discern or distinguish.^[1] This Greek word is formed from διά, meaning *apart*, and γινῶσκειν, meaning *to learn*.

Overview

Typically, a person with abnormal *symptoms* will consult a health care provider such as a physician, podiatrist, nurse practitioner, physical therapist or physicians assistant, who will then obtain a medical history of the patient's illness and perform a physical examination for *signs* of disease. The provider will formulate a hypothesis of likely diagnoses and in many cases will obtain further testing to confirm or clarify the diagnosis before providing treatment.

Medical tests commonly performed are measuring blood pressure, checking the pulse rate, listening to the heart with a stethoscope, urine tests, fecal tests, saliva tests, blood tests, medical imaging, electrocardiogram, hydrogen breath test and occasionally biopsy.

For instance, a common disorder such as pneumonia was nevertheless used as a diagnosis before the germ theory was accepted, and the disease was defined as a complex of many symptoms consisting of cough, sputum production, fever and chills. Later, as the actual cause was assigned to micro-organisms, the term diagnosis included the causality, e.g., pneumococcal pneumonia, suggesting not only a spectrum of symptoms but also a cause for the symptoms.

Advances in medicine could be described as a shift from definition #1 to definition #2 as scientific causalities were discovered. This differentiation of the term diagnosis is critically important because widespread disagreement exists between medical and psychiatric practitioners as to whether causalities for various diseases and disorders are known or not. If causalities are assumed to be known, then authentic cures can be obtained by correcting the causal abnormalities. If causalities are assumed to be unknown, then palliative treatments to reduce symptoms are the best treatments possible.

Diagnosis in medical practice

A provider's job is to know the human body and its functions in terms of normality (homeostasis). The four cornerstones of diagnostic medicine, each essential for understanding homeostasis, are: anatomy (the structure of the human body), physiology (how the body works), pathology (what can go wrong with the anatomy and physiology) and psychology (thought and behavior). Once the provider knows what is normal and can measure the patient's current condition against those norms, she or he can then determine the patient's particular departure from homeostasis and the degree of departure. This is called the **diagnosis**. Once a diagnosis has been reached, the provider is able to propose a management plan, which will include treatment as well as plans for follow-up. From this point on, in addition to treating the patient's condition, the provider educates the patient about the causes, progression, outcomes, and possible treatments of his ailments, as well as providing advice for maintaining health.

It should be noted however, that medical diagnosis in psychology or psychiatry is problematic. Apart from the fact that there are differing theoretical views toward mental conditions and that there are few "lab" tests available for various major disorders (e.g., clinical depression), a causal analysis with respect to symptomatology and disorder/disease is not always possible. As a result, most if not all mental conditions, function as both symptoms as

well as disorders. There are often functional descriptions provided for psychological disorders and these are vulnerable to circular reasoning due to the etiological fuzziness inherent of these diagnostic categories. (BDG, 2006)

Diagnostic procedure

The diagnostic process is fluid in which the provider gathers information from the patient and others, from a physical examination of the patient, and from medical tests performed upon the patient.

There are a number of techniques used by providers to obtain a correct diagnosis^[2]:

exhaustive method

every possible question is asked and all possible data is collected.

algorithmic method

the provider follows the steps of a proven strategy.

pattern-recognition method

the provider uses experience to recognise a pattern of clinical characteristics.

differential diagnosis

the provider uses the hypothetico-deductive method, a systematic, problem-focused method of inquiry.

The advanced clinician uses a combination of the pattern-recognition and hypothetico-deductive approaches.^[3]

The presence of some medical conditions cannot be established with complete confidence from examination or testing. Diagnosis is therefore by elimination of other reasonable possibilities, referred to as the diagnosis of exclusion.

The provider should consider the patient in their 'well' context rather than simply as a walking medical condition. This entails assessing the socio-political context of the patient (family, work, stress, beliefs), in addition to the patient's physical body, as this often offers vital clues to the patient's condition and its management.

The process of diagnosis begins when the patient consults the provider and presents a set of complaints (symptoms). If the patient is unconscious, this condition is the de facto complaint. The provider then obtains further information from the patient and from those who know him or her, if present, about the patient's symptoms, their previous state of health, living conditions, and so forth.

Rather than consider the myriad diseases that could afflict the patient, the provider narrows down the possibilities to their illnesses likely to account for the apparent symptoms, making a list of only those disease (conditions) that could account for what is wrong with the patient. These are generally ranked in order of probability.

The provider then conducts a physical examination of the patient, studies the patient's medical record, and asks further questions in an effort to rule out as many of the potential conditions as possible. When the list is narrowed down to a single condition, this is called the differential diagnosis and provides the basis for a hypothesis of what is ailing the patient.

Unless the provider is certain of the condition present, further medical tests are performed or scheduled such as medical imaging, in part to confirm or disprove the diagnosis but also to document the patient's status to keep the patient's medical history up to date. Consultations with other providers and specialists in the field may be sought. If unexpected findings are made during this process, the initial hypothesis may be ruled out and the provider must then consider other hypotheses.

Despite all of these complexities, most patient consultations are relatively brief, because many diseases are obvious, or the providers experience may enable him or her to recognize the condition quickly. Another factor is that the decision tree is used for most diagnostic hypothesis testing are relatively short.

Once the provider has completed the diagnosis, the prognosis is explained to the patient and a treatment plan is proposed which includes therapy and follow-up consultations and tests to monitor the condition and the progress of

the treatment, if needed, usually according to the medical guideline provided by the medical field on the treatment of the particular illness.

Treatment itself may indicate a need for review of the diagnosis if there is a failure to respond to treatments that would normally work.

A *laboratory diagnosis* is either a substitution or complement to the diagnosis made by examination of the patient. For instance, a proper diagnosis of infectious diseases usually requires both an examination of symptoms, as well as laboratory characteristics of the pathogen involved.

Diagnostic tests

A diagnostic test is any kind of medical test performed to aid in the diagnosis or detection of disease. The possible benefits of a diagnostic test must be weighed against the costs of unnecessary tests and resulting unnecessary follow-up and possibly even unnecessary treatment of incidental findings.^[4]

Diagnostic tests can have psychological effects on the patient that increase or reduce the symptoms.^{[5] [6]}

Overdiagnosis

Overdiagnosis is the diagnosis of "disease" that will never cause symptoms or death during a patient's lifetime. It is a problem because it turns people into patients unnecessarily and because it leads to treatments that can only cause harm. Overdiagnosis occurs when a disease is diagnosed correctly, but the diagnosis is irrelevant. A correct diagnosis may be irrelevant because treatment for the disease is not available, not needed, or not wanted.

Errors in diagnosis

Causes of error in diagnosis are:^[7]

- the manifestation of disease are not sufficiently noticeable
- a disease is omitted from consideration
- too much significance is given to some aspect of the diagnosis

Tools

Clinical decision support systems are interactive computer programs designed to assist health professionals with decision-making tasks. The clinician interacts with the software utilizing both the clinician's knowledge and the software to make a better analysis of the patients data than either human or software could make on their own. Typically the system makes suggestions for the clinician to look through and the clinician picks useful information and removes erroneous suggestions.^[8]

History

The history of medical diagnosis began in earnest from the days of Imhotep in ancient Egypt and Hippocrates in ancient Greece. In Traditional Chinese Medicine, there are four diagnostic methods: inspection, auscultation-olfaction, interrogation, and palpation.^[9] A Babylonian medical textbook, the *Diagnostic Handbook* written by Esagil-kin-apli (fl. 1069-1046 BC), introduced the use of empiricism, logic and rationality in the diagnosis of an illness or disease.^[10] The book made use of logical rules in combining observed symptoms on the body of a patient with its diagnosis and prognosis.^[11] Esagil-kin-apli described the symptoms for many varieties of epilepsy and related ailments along with their diagnosis and prognosis.^[12]

The practice of diagnosis continues to be dominated by theories set down in the early 20th century.

See also

- Diagnosis codes
- Diagnosis of exclusion
- Diagnosis-related group
- Diagnostic and Statistical Manual of Mental Disorders
- Doctor-patient relationship
- Etiology
- International Statistical Classification of Diseases and Related Health Problems (ICD)
- Medical classification
- Merck Manual of Diagnosis and Therapy
- Misdiagnosis and medical error
- Nosology
- Nursing diagnosis
- Overdiagnosis
- Pathogenesis
- Pathology
- Preimplantation genetic diagnosis
- Prenatal diagnosis
- Remote diagnostics
- Self diagnosis
- Trashcan diagnosis

Lists

- List of diseases
- List of medical symptoms
- List of disorders
- Category:Diseases

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External links

- The Merck Manuals Online Medical Library (<http://www.merck.com/mmpe/>)

Medical Imaging

Medical Imaging Techniques

Medical imaging is the technique and process used to create images of the human body (or parts and function thereof) for clinical purposes (medical procedures seeking to reveal, diagnose or examine disease) or medical science (including the study of normal anatomy and physiology). Although imaging of removed organs and tissues can be performed for medical reasons, such procedures are not usually referred to as medical imaging, but rather are a part of pathology.

As a discipline and in its widest sense, it is part of biological imaging and incorporates radiology (in the wider sense), nuclear medicine, investigative radiological sciences, endoscopy, (medical) thermography, medical photography and microscopy (e.g. for human pathological investigations).

Measurement and recording techniques which are not primarily designed to produce images, such as electroencephalography (EEG), magnetoencephalography (MEG), Electrocardiography (EKG) and others, but which produce data susceptible to be represented as maps (i.e. containing positional information), can be seen as forms of medical imaging.

Overview

In the clinical context, "invisible light" medical imaging is generally equated to radiology or "clinical imaging" and the medical practitioner responsible for interpreting (and sometimes acquiring) the images is a radiologist. "Visible light" medical imaging involves digital video or still pictures that can be seen without special equipment. Dermatology and wound care are two modalities that utilize visible light imagery. Diagnostic radiography designates the technical aspects of medical imaging and in particular the acquisition of medical images. The *radiographer* or *radiologic technologist* is usually responsible for acquiring medical images of diagnostic quality, although some radiological interventions are performed by radiologists. While radiology is an evaluation of anatomy, nuclear medicine provides functional assessment.

As a field of scientific investigation, medical imaging constitutes a sub-discipline of biomedical engineering, medical physics or medicine depending on the context: Research and development in the area of instrumentation, image acquisition (e.g. radiography), modelling and quantification are usually the preserve of biomedical engineering, medical physics and computer science; Research into the application and interpretation of medical images is usually the preserve of radiology and the medical sub-discipline relevant to medical condition or area of medical science (neuroscience, cardiology, psychiatry, psychology, etc.) under investigation. Many of the techniques developed for medical imaging also have scientific and industrial applications.

Medical imaging is often perceived to designate the set of techniques that noninvasively produce images of the internal aspect of the body. In this restricted sense, medical imaging can be seen as the solution of mathematical inverse problems. This means that cause (the properties of living tissue) is inferred from effect (the observed signal). In the case of ultrasonography the probe consists of ultrasonic pressure waves and echoes inside the tissue show the internal structure. In the case of projection radiography, the probe is X-ray radiation which is absorbed at different rates in different tissue types such as bone, muscle and fat.

The term noninvasive is a term based on the fact that following medical imaging modalities do not penetrate the skin physically. But on the electromagnetic and radiation level, they are quite invasive. From the high energy photons in X-Ray Computed Tomography, to the 2+ Tesla coils of an MRI device, these modalities alter the physical and chemical reactions of the body in order to obtain data.

Radiography

Two forms of radiographic images are in use in medical imaging; projection radiography and fluoroscopy, with the latter being useful for intraoperative and catheter guidance. These 2D techniques are still in wide use despite the advance of 3D tomography due to the low cost, high resolution, and depending on application, lower radiation dosages. This imaging modality utilizes a wide beam of x rays for image acquisition and is the first imaging technique available in modern medicine.

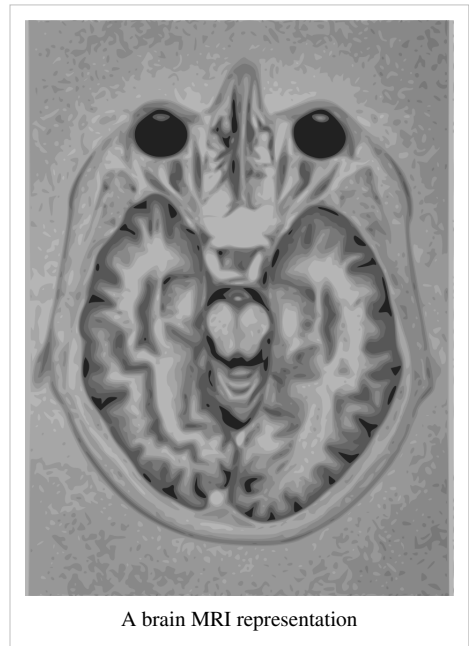
- *Fluoroscopy* produces real-time images of internal structures of the body in a similar fashion to radiography, but employs a constant input of x-rays, at a lower dose rate. Contrast media, such as barium, iodine, and air are used to visualize internal organs as they work. Fluoroscopy is also used in image-guided procedures when constant feedback during a procedure is required. An image receptor is required to convert the radiation into an image after it has passed through the area of interest. Early on this was a fluorescing screen, which gave way to an Image Amplifier (IA) which was a large vacuum tube that had the receiving end coated with cesium iodide, and a mirror at the opposite end. Eventually the mirror was replaced with a TV camera.
- *Projectional radiographs*, more commonly known as x-rays, are often used to determine the type and extent of a fracture as well as for detecting pathological changes in the lungs. With the use of radio-opaque contrast media, such as barium, they can also be used to visualize the structure of the stomach and intestines - this can help diagnose ulcers or certain types of colon cancer.

Magnetic resonance imaging (MRI)

A magnetic resonance imaging instrument (MRI scanner), or "nuclear magnetic resonance (NMR) imaging" scanner as it was originally known, uses powerful magnets to polarise and excite hydrogen nuclei (single proton) in water molecules in human tissue, producing a detectable signal which is spatially encoded, resulting in images of the body. MRI uses three electromagnetic fields: a very strong (on the order of units of teslas) static magnetic field to polarize the hydrogen nuclei, called the static field; a weaker time-varying (on the order of 1 kHz) field(s) for spatial encoding, called the gradient field(s); and a weak radio-frequency (RF) field for manipulation of the hydrogen nuclei to produce measurable signals, collected through an RF antenna.

Like CT, MRI traditionally creates a two dimensional image of a thin "slice" of the body and is therefore considered a tomographic imaging technique. Modern MRI instruments are capable of producing images in the form of 3D blocks, which may be considered a generalisation of the single-slice, tomographic, concept. Unlike CT, MRI does not involve the use of ionizing radiation and is therefore not associated with the same health hazards. For example, because MRI has only been in use since the early 1980s, there are no known long-term effects of exposure to strong static fields (this is the subject of some debate; see 'Safety' in MRI) and therefore there is no limit to the number of scans to which an individual can be subjected, in contrast with X-ray and CT. However, there are well-identified health risks associated with tissue heating from exposure to the RF field and the presence of implanted devices in the body, such as pace makers. These risks are strictly controlled as part of the design of the instrument and the scanning protocols used.

Because CT and MRI are sensitive to different tissue properties, the appearance of the images obtained with the two techniques differ markedly. In CT, X-rays must be blocked by some form of dense tissue to create an image, so the image quality when looking at soft tissues will be poor. In MRI, while any nucleus with a net nuclear spin can be



A brain MRI representation

used, the proton of the hydrogen atom remains the most widely used, especially in the clinical setting, because it is so ubiquitous and returns a large signal. This nucleus, present in water molecules, allows the excellent soft-tissue contrast achievable with MRI.

Nuclear medicine

Nuclear medicine encompasses both diagnostic imaging and treatment of disease, and may also be referred to as molecular medicine or molecular imaging & therapeutics^[1]. Nuclear medicine uses certain properties of isotopes and the energetic particles emitted from radioactive material to diagnose or treat various pathology. Different from the typical concept of anatomic radiology, nuclear medicine enables assessment of physiology. This function-based approach to medical evaluation has useful applications in most subspecialties, notably oncology, neurology, and cardiology. *Gamma cameras* are used in e.g. scintigraphy, SPECT and PET to detect regions of biologic activity that may be associated with disease. Relatively short lived isotope, such as ^{123}I is administered to the patient. Isotopes are often preferentially absorbed by biologically active tissue in the body, and can be used to identify tumors or fracture points in bone. Images are acquired after collimated photons are detected by a crystal that gives off a light signal, which is in turn amplified and converted into count data.

- *Scintigraphy* ("scint") is a form of diagnostic test wherein radioisotopes are taken internally, for example intravenously or orally. Then, gamma camera capture and form two-dimensional^[2] images from the radiation emitted by the radiopharmaceuticals. For example, technetium-labeled isoniazid (INH) and ethambutol (EMB) has been used for tubercular imaging for early diagnosis of tuberculosis^[3].
 - *SPECT* is a 3D tomographic technique that uses gamma camera data from many projections and can be reconstructed in different planes. A dual detector head gamma camera combined with a CT scanner, which provides localization of functional SPECT data, is termed a SPECT/CT camera, and has shown utility in advancing the field of molecular imaging. In most other medical imaging modalities, energy is passed through the body and the reaction or result is read by detectors. In SPECT imaging, the patient is injected with a radioisotope, most commonly Thallium 201TI, Technetium 99mTC, Iodine 123I, and Gallium 68Ga^[4].
- . The radioactive gamma rays are emitted through the body as the natural decaying process of these isotopes takes place. The emissions of the gamma rays are captured by detectors that surround the body. This essentially means that the human is now the source of the radioactivity, rather than the medical imaging devices such as X-Ray, CT, or Ultrasound.
- *Positron emission tomography* (PET) uses coincidence detection to image functional processes. Short-lived positron emitting isotope, such as ^{18}F , is incorporated with an organic substance such as glucose, creating F18-fluorodeoxyglucose, which can be used as a marker of metabolic utilization. Images of activity distribution throughout the body can show rapidly growing tissue, like tumor, metastasis, or infection. PET images can be viewed in comparison to computed tomography scans to determine an anatomic correlate. Modern scanners combine PET with a CT, or even MRI, to optimize the image reconstruction involved with positron imaging. This is performed on the same equipment without physically moving the patient off of the gantry. The resultant hybrid of functional and anatomic imaging information is a useful tool in non-invasive diagnosis and patient management.

Photoacoustic imaging

Photoacoustic imaging is a recently developed hybrid biomedical imaging modality based on the photoacoustic effect. It combines the advantages of optical absorption contrast with ultrasonic spatial resolution for deep imaging in (optical) diffusive or quasi-diffusive regime. Recent studies have shown that photoacoustic imaging can be used in vivo for tumor angiogenesis monitoring, blood oxygenation mapping, functional brain imaging, and skin melanoma detection, etc.

Breast Thermography

Digital infrared imaging thermography is based on the principle that metabolic activity and vascular circulation in both pre-cancerous tissue and the area surrounding a developing breast cancer is almost always higher than in normal breast tissue. Cancerous tumors require an ever-increasing supply of nutrients and therefore increase circulation to their cells by holding open existing blood vessels, opening dormant vessels, and creating new ones (neoangiogenesis). This process frequently results in an increase in regional surface temperatures of the breast. Digital infrared imaging uses extremely sensitive medical infrared cameras and sophisticated computers to detect, analyze, and produce high-resolution diagnostic images of these temperature variations. Because of DII's sensitivity, these temperature variations may be among the earliest signs of breast cancer and/or a pre-cancerous state of the breast^[5].

Tomography

Tomography is the method of imaging a single plane, or slice, of an object resulting in a tomogram. There are several forms of tomography:

- **Linear tomography:** This is the most basic form of tomography. The X-ray tube moved from point "A" to point "B" above the patient, while the cassette holder (or "bucky") moves simultaneously under the patient from point "B" to point "A." The fulcrum, or pivot point, is set to the area of interest. In this manner, the points above and below the focal plane are blurred out, just as the background is blurred when panning a camera during exposure. No longer carried out and replaced by computed tomography.
- **Poly tomography:** This was a complex form of tomography. With this technique, a number of geometrical movements were programmed, such as hypocycloidal, circular, figure 8, and elliptical. Philips Medical Systems [6] produced one such device called the 'Polytome.' This unit was still in use into the 1990s, as its resulting images for small or difficult physiology, such as the inner ear, was still difficult to image with CTs at that time. As the resolution of CTs got better, this procedure was taken over by the CT.
- **Zonography:** This is a variant of linear tomography, where a limited arc of movement is used. It is still used in some centres for visualising the kidney during an intravenous urogram (IVU).
- **Orthopantomography (OPT or OPG):** The only common tomographic examination in use. This makes use of a complex movement to allow the radiographic examination of the mandible, as if it were a flat bone. It is often referred to as a "Panorex", but this is incorrect, as it is a trademark of a specific company.
- **Computed Tomography (CT), or Computed Axial Tomography (CAT:** A CT scan, also known as a CAT scan), is a helical tomography (latest generation), which traditionally produces a 2D image of the structures in a thin section of the body. It uses X-rays. It has a greater ionizing radiation dose burden than projection radiography; repeated scans must be limited to avoid health effects. CT is based on the same principles as X-Ray projections but in this case, the patient is enclosed in a surrounding ring of detectors assigned with 500-1000 scintillation detectors^[4]

. This being the fourth-generation X-Ray CT scanner geometry. Previously in older generation scanners, the X-Ray beam was paired by a translating source and detector.

Ultrasound

Medical ultrasonography uses high frequency broadband sound waves in the megahertz range that are reflected by tissue to varying degrees to produce (up to 3D) images. This is commonly associated with imaging the fetus in pregnant women. Uses of ultrasound are much broader, however. Other important uses include imaging the abdominal organs, heart, breast, muscles, tendons, arteries and veins. While it may provide less anatomical detail than techniques such as CT or MRI, it has several advantages which make it ideal in numerous situations, in particular that it studies the function of moving structures in real-time, emits no ionizing radiation, and contains speckle that can be used in elastography. Ultrasound is also used as a popular research tool for capturing raw data,

that can be made available through an Ultrasound research interface, for the purpose of tissue characterization and implementation of new image processing techniques. The concepts of ultrasound differ from other medical imaging modalities in the fact that it is operated by the transmission and receipt of sound waves. The high frequency sound waves are sent into the tissue and depending on the composition of the different tissues; the signal will be attenuated and returned at separate intervals. A path of reflected sound waves in a multilayered structure can be defined by an input acoustic impedance(Ultrasound sound wave) and the Reflection and transmission coefficients of the relative structures^[4] . It is very safe to use and does not appear to cause any adverse effects, although information on this is not well documented. It is also relatively inexpensive and quick to perform. Ultrasound scanners can be taken to critically ill patients in intensive care units, avoiding the danger caused while moving the patient to the radiology department. The real time moving image obtained can be used to guide drainage and biopsy procedures. Doppler capabilities on modern scanners allow the blood flow in arteries and veins to be assessed.

Medical imaging topics

Maximizing imaging procedure use

The amount of data obtained in a single MR or CT scan is very extensive. Some of the data that radiologists discard could save patients time and money, while reducing their exposure to radiation and risk of complications from invasive procedures.^[7]

Creation of three-dimensional images

Recently, techniques have been developed to enable CT, MRI and ultrasound scanning software to produce 3D images for the physician.^[8] Traditionally CT and MRI scans produced 2D static output on film. To produce 3D images, many scans are made, then combined by computers to produce a 3D model, which can then be manipulated by the physician. 3D ultrasounds are produced using a somewhat similar technique. In diagnosing disease of the viscera of abdomen,ultrasound is particularly sensitive on imaging of biliary tract,urinary tract and female reproductive organs(ovary,fallopian tubes).As for example,diagnosis of gall stone by dilatation of common bile duct and stone in common bile duct . With the ability to visualize important structures in great detail, 3D visualization methods are a valuable resource for the diagnosis and surgical treatment of many pathologies. It was a key resource for the famous, but ultimately unsuccessful attempt by Singaporean surgeons to separate Iranian twins Ladan and Laleh Bijani in 2003. The 3D equipment was used previously for similar operations with great success.

Other proposed or developed techniques include:

- Diffuse optical tomography
- Elastography
- Electrical impedance tomography
- Optoacoustic imaging
- Ophthalmology
 - A-scan
 - B-scan
 - Corneal topography
 - Optical coherence tomography
 - Scanning laser ophthalmoscopy

Some of these techniques are still at a research stage and not yet used in clinical routines.

Compression of medical images

Medical imaging techniques produce very large amounts of data, especially from CT, MRI and PET modalities. As a result, storage and communications of electronic image data are prohibitive without the use of compression. JPEG 2000 is the state-of-the-art image compression DICOM standard for storage and transmission of medical images. The cost and feasibility of accessing large image data sets over low or various bandwidths are further addressed by use of another DICOM standard, called JPIP, to enable efficient streaming of the JPEG 2000 compressed image data.

Non-diagnostic imaging

Neuroimaging has also been used in experimental circumstances to allow people (especially disabled persons) to control outside devices, acting as a brain computer interface.

Archiving and recording

Used primarily in ultrasound imaging, capturing the image a medical imaging device is required for archiving and telemedicine applications. In most scenarios, a frame grabber is used in order to capture the video signal from the medical device and relay it to a computer for further processing and operations.^[9]

Open source software for medical image analysis

Several open source software packages are available for performing analysis of medical images:

- ImageJ
- 3D Slicer
- ITK
- OsiriX
- GemIdent
- MicroDicom
- FreeSurfer

Use in pharmaceutical clinical trials

Medical imaging has become a major tool in clinical trials since it enables rapid diagnosis with visualization and quantitative assessment.

A typical clinical trial goes through multiple phases and can take up to eight years. Clinical endpoints or outcomes are used to determine whether the therapy is safe and effective. Once a patient reaches the endpoint, he/she is generally excluded from further experimental interaction. Trials that rely solely on clinical endpoints are very costly as they have long durations and tend to need large number of patients.

In contrast to clinical endpoints, surrogate endpoints have been shown to cut down the time required to confirm whether a drug has clinical benefits. Imaging biomarkers (a characteristic that is objectively measured by an imaging technique, which is used as an indicator of pharmacological response to a therapy) and surrogate endpoints have shown to facilitate the use of small group sizes, obtaining quick results with good statistical power.^[10]

Imaging is able to reveal subtle change that is indicative of the progression of therapy that may be missed out by more subjective, traditional approaches. Statistical bias is reduced as the findings are evaluated without any direct patient contact.

For example, measurement of tumour shrinkage is a commonly used surrogate endpoint in solid tumour response evaluation. This allows for faster and more objective assessment of the effects of anticancer drugs. In evaluating the extent of Alzheimer's disease, it is still prevalent to use behavioural and cognitive tests. MRI scans on the entire brain can accurately pinpoint hippocampal atrophy rate while PET scans is able to measure the brain's metabolic activity by measuring regional glucose metabolism.^[10]

An imaging-based trial will usually be made up of three components:

1. A realistic imaging protocol. The protocol is an outline that standardizes (as far as practically possible) the way in which the images are acquired using the various modalities (PET, SPECT, CT, MRI). It covers the specifics in which images are to be stored, processed and evaluated.
2. An imaging centre that is responsible for collecting the images, perform quality control and provide tools for data storage, distribution and analysis. It is important for images acquired at different time points are displayed in a standardised format to maintain the reliability of the evaluation. Certain specialised imaging contract research organizations provide to end medical imaging services, from protocol design and site management through to data quality assurance and image analysis.
3. Clinical sites that recruit patients to generate the images to send back to the imaging centre.

See also

- Preclinical imaging
- Cardiac PET
- Biomedical informatics
- Digital Imaging and Communications in Medicine
- Digital Mammography and PACS
- EMMI European Master in Molecular Imaging
- eMix
- Fotofinder
- Full-body scan
- VoluMedic
- Magnetic field imaging
- Medical examination
- Medical radiography
- Medical test
- Neuroimaging
- Non-invasive (medical)
- PACS
- JPEG 2000 compression
- JPIP streaming
- Pneumoencephalogram
- Radiology information system
- Segmentation (image processing)
- Signal-to-noise ratio
- Society for Imaging Science and Technology
- Tomogram
- Virtopsy

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External links

- Medical imaging (<http://www.dmoz.org/Health/Medicine/Imaging/>) at the Open Directory Project
- Medical Image Database (<http://rad.usuhs.edu/medpix/index.html?>) Free Indexed Online Images
- <http://www.aware.com/imaging/accuradjpip.htm> What is JPIP?

Radiology

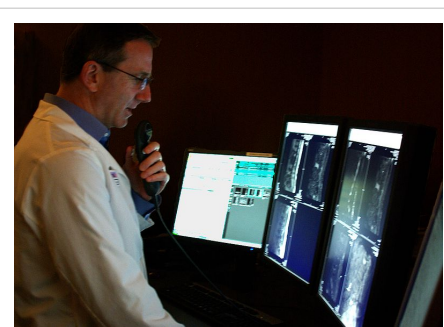
Radiology is the branch of science where scientists use x-rays to see the inside of the human body from different rays. Radiologists utilize an array of imaging technologies (such as ultrasound, computed tomography (CT), nuclear medicine, positron emission tomography (PET) and magnetic resonance imaging (MRI)) to diagnose or treat diseases. Interventional radiology is the performance of (usually minimally invasive) medical procedures with the guidance of imaging technologies. The acquisition of medical imaging is usually carried out by the radiographer or radiologic technologist.

Acquisition of radiological images

The following imaging modalities are used in the field of diagnostic radiology:

Projection (plain) radiography

Radiographs (or roentgenographs, named after the discoverer of x-rays, Wilhelm Conrad Röntgen) are produced by the transmission of x-rays through a patient to a capture device then converted into an image for diagnosis. The original and still common imaging produces silver impregnated films. In Film-Screen radiography an x-ray tube generates a beam of x-rays which is aimed at the patient. The x-rays which pass through the patient are filtered to reduce scatter and noise and then strike an undeveloped film, held tight to a screen of light emitting phosphors in a light-tight cassette. The film is then developed chemically and an image appears on the film. Now replacing Film-Screen radiography is Digital Radiography, DR, in which x-rays strike a plate of sensors which then converts the signals generated into digital information and an image on computer screen. Plain radiography was the only imaging modality available during the first 50 years of radiology. It is still the first study ordered in evaluation of the lungs, heart and skeleton because of its wide availability, speed and relative low cost.



A radiologist interprets medical images on a modern Picture archiving and communication system (PACS) workstation. San Diego, CA, 2010.



Madura Foot X-Ray

Fluoroscopy

Fluoroscopy and angiography are special applications of X-ray imaging, in which a fluorescent screen and image intensifier tube is connected to a closed-circuit television system.^[1] :26 This allows real-time imaging of structures in motion or augmented with a radiocontrast agent. Radiocontrast agents are administered, often swallowed or injected into the body of the patient, to delineate anatomy and functioning of the blood vessels, the genitourinary system or the gastrointestinal tract. Two radiocontrasts are presently in use. Barium (as BaSO_4) may be given orally or rectally for evaluation of the GI tract. Iodine, in multiple proprietary forms, may be given by oral, rectal, intraarterial or intravenous routes. These radiocontrast agents strongly absorb or scatter X-ray radiation, and in conjunction with the real-time imaging allows demonstration of dynamic processes, such as peristalsis in the digestive tract or blood flow in arteries and veins. Iodine contrast may also be concentrated in abnormal areas more or less than in normal tissues and make abnormalities (tumors, cysts, inflammation) more conspicuous. Additionally, in specific circumstances air can be used as a contrast agent for the gastrointestinal system and carbon dioxide can be used as a contrast agent in the venous system; in these cases, the contrast agent attenuates the X-ray radiation less than the surrounding tissues.

Interventional radiology

Interventional radiology (abbreviated **IR** or sometimes **VIR** for **vascular and interventional radiology**, also known as Surgical Radiology or Image-Guided Surgery) is a subspecialty of radiology in which minimally invasive procedures are performed using **image guidance**. Some of these procedures are done for purely diagnostic purposes (e.g., angiogram), while others are done for treatment purposes (e.g., angioplasty).

The basic concept behind interventional radiology is to diagnose or treat pathology with the most minimally invasive technique possible. Interventional radiologists diagnose and treat several disorders including peripheral vascular disease, renal artery stenosis, inferior vena cava filter placement, gastrostomy tube placements, biliary stents and hepatic interventions. Images are used for guidance and the primary instruments used during the procedure are needles and tiny tubes called catheters. The images provide road maps that allow the interventional radiologist to guide these instruments through the body to the areas containing disease. By minimizing the physical trauma to the patient, peripheral interventions can reduce infection rates and recovery time as well as shorten hospital stays. To be a trained interventionalist in the United States, an individual typically requires fifteen years of post-high school training, of which seven years is spent in residency.^[2]

CT scanning

CT imaging uses X-rays in conjunction with computing algorithms to image the body.^[3] In CT, an X-ray generating tube opposite an X-ray detector (or detectors) in a ring shaped apparatus rotate around a patient producing a computer generated cross-sectional image (tomogram). CT is acquired in the axial plane, while coronal and sagittal images can be rendered by computer reconstruction. Radiocontrast agents are often used with CT for enhanced delineation of anatomy. Although radiographs provide higher spatial resolution, CT can detect more subtle variations in attenuation of X-rays. CT exposes the patient to more ionizing radiation than a radiograph.

Spiral Multi-detector CT utilizes 8, 16, 64 or more detectors during continuous motion of the patient through the radiation beam to obtain much finer detail images in a shorter exam time. With rapid administration of IV contrast during the CT scan these fine detail images can be reconstructed into 3D images of carotid, cerebral and coronary arteries, CTA, CT angiography.



Brain CT Scan image slice

CT scanning has become the test of choice in diagnosing some urgent and emergent conditions such as cerebral hemorrhage, pulmonary embolism (clots in the arteries of the lungs), aortic dissection (tearing of the aortic wall), appendicitis, diverticulitis, and obstructing kidney stones. Continuing improvements in CT technology including faster scanning times and improved resolution have dramatically increased the accuracy and usefulness of CT scanning and consequently increased utilization in medical diagnosis.

The first commercially viable CT scanner was invented by Sir Godfrey Hounsfield at EMI Central Research Labs, Great Britain in 1972. EMI owned the distribution rights to The Beatles music and it was their profits which funded the research.^[4] Sir Hounsfield and Alan McLeod McCormick shared the Nobel Prize for Medicine in 1979 for the invention of CT scanning. The first CT scanner in North America was installed at the Mayo Clinic in Rochester, MN in 1972.

Ultrasound

Medical ultrasonography uses ultrasound (high-frequency sound waves) to visualize soft tissue structures in the body in real time. No ionizing radiation is involved, but the quality of the images obtained using ultrasound is highly dependent on the skill of the person (ultrasonographer) performing the exam. Ultrasound is also limited by its inability to image through air (lungs, bowel loops) or bone. The use of ultrasound in medical imaging has developed mostly within the last 30 years. The first ultrasound images were static and two dimensional (2D), but with modern-day ultrasonography 3D reconstructions can be observed in real-time; effectively becoming 4D. Marko is a radiologist.

Because ultrasound does not utilize ionizing radiation, unlike radiography, CT scans, and nuclear medicine imaging techniques, it is generally considered safer. For this reason, this modality plays a vital role in obstetrical imaging. Fetal anatomic development can be thoroughly evaluated allowing early diagnosis of many fetal anomalies. Growth can be assessed over time, important in patients with chronic disease or gestation-induced disease, and in multiple gestations (twins, triplets etc.). Color-Flow Doppler Ultrasound measures the severity of peripheral vascular disease and is used by Cardiology for dynamic evaluation of the heart, heart valves and major vessels. Stenosis of the carotid arteries can presage cerebral infarcts (strokes). DVT in the legs can be found via ultrasound before it dislodges and travels to the lungs (pulmonary embolism), which can be fatal if left untreated. Ultrasound is useful for image-guided interventions like biopsies and drainages such as thoracentesis). Small portable ultrasound devices now replace peritoneal lavage in the triage of trauma victims by directly assessing for the presence of hemorrhage in the peritoneum and the integrity of the major viscera including the liver, spleen and kidneys. Extensive hemoperitoneum (bleeding inside the body cavity) or injury to the major organs may require emergent surgical exploration and repair.

MRI (Magnetic Resonance Imaging)

MRI uses strong magnetic fields to align atomic nuclei (usually hydrogen protons) within body tissues, then uses a radio signal to disturb the axis of rotation of these nuclei and observes the radio frequency signal generated as the nuclei return to their baseline states plus all surrounding areas. The radio signals are collected by small antennae, called coils, placed near the area of interest. An advantage of MRI is its ability to produce images in axial, coronal, sagittal and multiple oblique planes with equal ease. MRI scans give the best soft tissue contrast of all the imaging modalities. With advances in scanning speed and spatial resolution, and improvements in computer 3D algorithms and hardware, MRI has become a tool in musculoskeletal radiology and neuroradiology.

One disadvantage is that the patient has to hold still for long periods of time in a noisy, cramped space while the imaging is performed.

Claustrophobia severe enough to terminate the MRI exam is reported in up to 5% of patients. Recent improvements in magnet design including stronger magnetic fields (3 teslas), shortening exam times, wider, shorter magnet bores and more open magnet designs, have brought some relief for claustrophobic patients. However, in magnets of equal field strength there is often a trade-off between image quality and open design. MRI has great benefit in imaging the brain, spine, and musculoskeletal system. The modality is currently contraindicated for patients with pacemakers, cochlear implants, some indwelling medication pumps, certain types of cerebral aneurysm clips, metal fragments in the eyes and some metallic hardware due to the powerful magnetic fields and strong fluctuating radio signals the body is exposed to. Areas of potential advancement include functional imaging, cardiovascular MRI, as well as MR image guided therapy.



MRI image of human knee with a displaced patella

Nuclear Medicine

Nuclear medicine imaging involves the administration into the patient of radiopharmaceuticals consisting of substances with affinity for certain body tissues labeled with radioactive tracer. The most commonly used tracers are Technetium-99m, Iodine-123, Iodine-131, Gallium-67 and Thallium-201. The heart, lungs, thyroid, liver, gallbladder, and bones are commonly evaluated for particular conditions using these techniques. While anatomical detail is limited in these studies, nuclear medicine is useful in displaying physiological function. The excretory function of the kidneys, iodine concentrating ability of the thyroid, blood flow to heart muscle, etc. can be measured. The principal imaging device is the gamma camera which detects the radiation emitted by the tracer in the body and displays it as an image. With computer processing, the information can be displayed as axial, coronal and sagittal images (SPECT images, single-photon emission computed tomography). In the most modern devices Nuclear Medicine images can be fused with a CT scan taken quasi-simultaneously so that the physiological information can be overlaid or co-registered with the anatomical structures to improve diagnostic accuracy.

Positron emission tomography (PET), scanning also falls under "nuclear medicine." In PET scanning, a radioactive, biologically active substance, most often Fludeoxyglucose (18F), is injected into a patient and the radiation emitted by the patient is detected to produce multi-planar images of the body. Metabolically more active tissues, such as cancer, concentrate the active substance more than normal tissues. PET images can be combined (or "fused") with an anatomic imaging study (currently generally CT images), to more accurately localize PET findings and thereby improve diagnostic accuracy.

Teleradiology

Teleradiology is the transmission of radiographic images from one location to another for interpretation by a radiologist. It is most often used to allow rapid interpretation of emergency room, ICU and other emergent examinations after hours of usual operation, at night and on weekends. In these cases the images are often sent across time zones (i.e. to Spain, Australia, India) with the receiving radiologist working his normal daylight hours. Teleradiology can also be utilized to obtain consultation with an expert or sub-specialist about a complicated or puzzling case.

Teleradiology requires a sending station, high speed Internet connection and high quality receiving station. At the transmission station, plain radiographs are passed through a digitizing machine before transmission, while CT scans, MRIs, Ultrasounds and Nuclear Medicine scans can be sent directly as they are already a stream of digital data. The computer at the receiving end will need to have a high-quality display screen that has been tested and cleared for clinical purposes. The interpreting radiologist then faxes or e-mails the radiology report to the requesting physician.

The major advantage of teleradiology is the ability to utilize different time zones to provide real-time emergency radiology services around-the-clock. The disadvantages include higher costs, limited contact between the ordering physician and the radiologist, and the inability to cover for procedures requiring an onsite radiologist. Laws and regulations concerning the use of teleradiology vary among the states, with some states requiring a license to practice medicine in the state sending the radiologic exam. Some states require the teleradiology report to be preliminary with the official report issued by a hospital staff radiologist.

Radiologist training

United States

Radiology is a competitive field in medicine and successful applicants are often near the top of their medical school class, with high board scores. The field is rapidly expanding due to advances in computer technology, which is closely linked to modern imaging. Diagnostic radiologists must complete at least 13 years of post-high school education, including 4 years of prerequisite undergraduate training, 4 years of medical school, and 5 years of post-graduate training. The first postgraduate year is usually a transitional year of various rotations, but is sometimes a preliminary internship in medicine or surgery. A four-year diagnostic radiology residency follows. The Radiology resident must pass a medical physics board exam covering the science and technology of ultrasound, CTs, x-rays, nuclear medicine and MRI. Core knowledge of the radiologist includes radiobiology, which is the study of the effects of ionizing radiation on living tissue. Near the completion of residency, the radiologist in training is eligible to take the written and oral board examinations administered by the American Board of Radiology (ABR). Starting in 2010, the ABR's board examination structure will be changed to include two computer-based exams, one given after the third year of residency training, and the second given 18 months after the first.

The Wayne State University School of Medicine and the University of South Carolina School of Medicine both offer an integrated radiology curriculum during their respective MD Programs in collaboration with GE Medical led by investigators of the Advanced Diagnostic Ultrasound in Microgravity study.^{[5] [6] [7]}

Following completion of residency training, radiologists either begin their practice or enter into sub-speciality training programs known as fellowships. Examples of sub-speciality training in radiology include abdominal imaging, thoracic imaging, CT/Ultrasound, MRI, musculoskeletal imaging, interventional radiology, neuroradiology, interventional neuroradiology, paediatric radiology, mammography and women's imaging. Fellowship training programs in radiology are usually 1 or 2 years in length.^[8]

Radiographic exams are usually performed by radiologic technologists, (also known as diagnostic radiographers) who in the United States have a 2-year Associates Degree and the UK a 3 year Honours Degree.

Veterinary radiologists are veterinarians that specialize in the use of X-rays, ultrasound, MRI and nuclear medicine for diagnostic imaging or treatment of disease in animals. They are certified in either diagnostic radiology or radiation oncology by the American College of Veterinary Radiology.

Germany

After obtaining medical licensure, German radiologists complete a 5-year residency, culminating with a board examination (known as Facharzt Ausbildung).

Italy

Until 2008, a Radiology training program had a duration of four years. At present, a radiology training program lasts five years. Further training is required for specialization in radiotherapy or nuclear medicine.

See also

- X-ray image intensifier (C-Arm), equipment that uses x-rays to produce an image feed displayed on a TV screen
- Digital Mammography and PACS
- Interventional radiology, in which minimally invasive procedures are performed using image guidance
- Medical radiography, the use of ionizing electromagnetic radiation, such as X-rays, in medicine
- Positron emission tomography, which produces a three-dimensional image
- Radiobiology, the interdisciplinary science that studies the biological effects of ionizing and non-ionizing radiation of the whole electromagnetic spectrum
- Radiation protection, the science of protecting people and the environment from the harmful effects of ionizing radiation
- Radiography, the use of X-rays to view unseen or hard-to-image objects
- Radiosensitivity, the susceptibility of organic tissues to the harmful effect of ionizing radiation
- Teleradiology, the transmission by electronic means of radiological patient images from one location to another for interpretation or consultation
- Radiology technician

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 - [5] http://www.gehealthcare.com/us/en/ultrasound/genimg/products/logiq_e/hryfrdhosp_waynestuni.html
 - [6] http://www.gehealthcare.com/us/en/ultrasound/genimg/products/logiq_e/med_schoolprg.html
 - [7] <http://www.jultrasoundmed.org/cgi/content/abstract/27/5/745>
 - [8] <http://www.healthsystem.virginia.edu/internet/radiology/educ-opps/fellowships.cfm>
-

External links

- Radiology (http://www.dmoz.org/Health/Medicine/Medical_Specialties/Radiology/) at the Open Directory Project
- MedPix medical imaging database (<http://rad.usuhs.edu/medpix/medpix.html?mode=default>)
- MedWorm (<http://www.medworm.com/rss/Radiology-37.php>) Radiology directory
- MyPACS medical imaging database (<http://mypacs.net>)
- Radiolopolis (<http://www.Radiolopolis.com>) an international Radiology community for education, research and clinical practice
- radRounds Radiology Network (<http://www.radrounds.com>) - Professional and Social Network for Radiology
- DSCT.com (<http://www.dsct.com>) international dual source CT experts community for education, research and clinical practice

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Molecular imaging

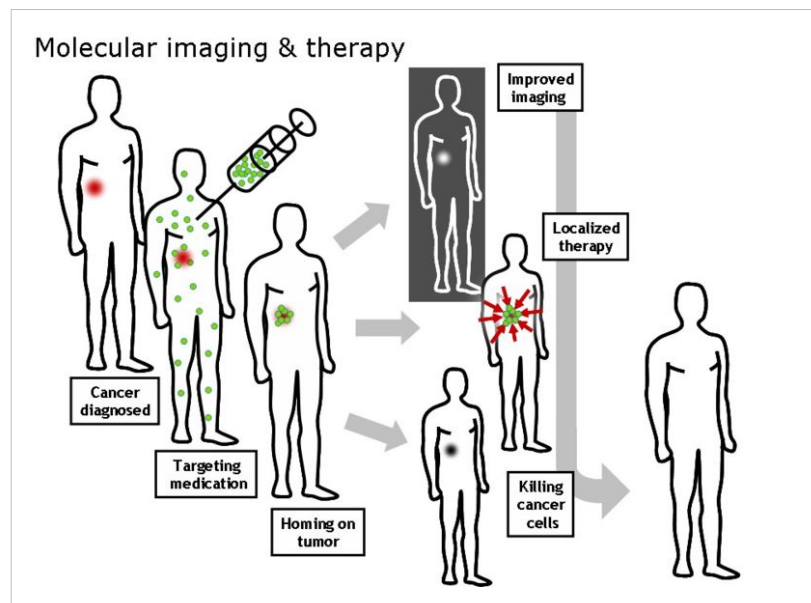
Molecular imaging originated from the field of radiopharmacology due to the need to better understand the fundamental molecular pathways inside organisms in a noninvasive manner.

Overview

Molecular Imaging emerged in the early twenty-first century as a discipline at the intersection of molecular biology and *in vivo* imaging. It enables the visualisation of the cellular function and the follow-up of the molecular process in living

organisms without perturbing them. The multiple and numerous potentialities of this field are applicable to the diagnosis of diseases such as cancer, and neurological and cardiovascular diseases. This technique also contributes to improving the treatment of these disorders by optimizing the pre-clinical and clinical tests of new medication. They are also expected to have a major economic impact due to earlier and more precise diagnosis. Molecular and Functional Imaging has taken on a new direction since the description of the human genome. New paths in fundamental research, as well as in applied and industrial research, render the task of scientists more complex and increase the demands on them. Therefore, a tailor-made teaching program is in order.

Molecular imaging differs from traditional imaging in that probes known as biomarkers are used to help image particular targets or pathways. Biomarkers interact chemically with their surroundings and in turn alter the image according to molecular changes occurring within the area of interest. This process is markedly different from previous methods of imaging which primarily imaged differences in qualities such as density or water content. This ability to image fine molecular changes opens up an incredible number of exciting possibilities for medical application, including early detection and treatment of disease and basic pharmaceutical development. Furthermore, molecular imaging allows for quantitative tests, imparting a greater degree of objectivity to the study of these areas.



One emerging technology is MALDI molecular imaging based on mass spectrometry. Many areas of research are being conducted in the field of molecular imaging. Much research is currently centered around detecting what is known as a predisease state or molecular states that occur before typical symptoms of a disease are detected. Other important veins of research are the imaging of gene expression and the development of novel biomarkers. Organizations such as the SNM Molecular Imaging Center of Excellence (MICoE) have formed to support research in this field. In Europe, other "networks of excellence" such as DiMI (Diagnostics in Molecular Imaging) or EMIL (European Molecular Imaging Laboratories) work on this new science, integrating activities and research in the field. In this way, a European Master Programme "EMMI" is being set up to train a new generation of professionals in molecular imaging.

Recently the term "Molecular Imaging" has been applied to a variety of microscopy and nanoscopy techniques including live-cell microscopy, Total Internal Reflection Fluorescence (TIRF)-microscopy, STimulated Emission Depletion (STED)-nanoscopy and Atomic Force Microscopy (AFM) as here images of molecules are the readout.

Imaging modalities

There are many different modalities that can be used for noninvasive molecular imaging. Each have their different strengths and weaknesses and some are more adept at imaging multiple targets than others.

Magnetic resonance imaging (MRI)

MRI has the advantages of having very high spatial resolution and is very adept at morphological imaging and functional imaging. MRI does have several disadvantages though. First, MRI has a sensitivity of around 10^{-3} mol/L to 10^{-5} mol/L which compared to other types of imaging can be very limiting. This problem stems from the fact that the difference between atoms in the high energy state and the low energy state is very small. For example at 1.5 teslas the difference between high and low energy states is approximately 9 molecules per 2 million. Improvements to increase MR sensitivity include hyperpolarization by increasing magnetic field strength, optical pumping, or dynamic nuclear polarization. There are also a variety of signal amplification schemes based on chemical exchange that increase sensitivity.

Optical imaging

There are a number of approaches used for optical imaging. The various methods depend upon fluorescence, bioluminescence, absorption or reflectance as the source of contrast.^[1]

Optical imaging's most valuable attribute is that it and ultrasound do not have strong safety concerns like the other medical imaging modalities.

The downside of optical imaging is the lack of penetration depth, especially when working at visible wavelengths. Depth of penetration is related to the absorption and scattering of light, which is primarily a function of the wavelength of the excitation source. Light is absorbed by endogenous chromophores found in living tissue (e.g. hemoglobin, melanin, and lipids). In general, light absorption and scattering decreases with increasing wavelength. Below ~700 nm (e.g. visible wavelengths), these effects result in shallow penetration depths of only a few millimeters. Thus, in the visible region of the spectrum, only superficial assessment of tissue features is possible. Above 900 nm, water absorption can interfere with signal-to-background ratio. Because the absorption coefficient of tissue is considerably lower in the near infrared (NIR) region (700-900 nm), light can penetrate more deeply, to depths of several centimeters.^[2]

Fluorescent probes and labels are an important tool for optical imaging. A number of near-infrared (NIR) fluorophores have been employed for in vivo imaging, including Kodak X-SIGHT Dyes and Conjugates, DyLight 750 and 800 Fluors, Cy 5.5 and 7 Fluors, Alexa Fluor 680 and 750 Dyes, IRI dye 680 and 800CW Fluors. Quantum dots, with their photostability and bright emissions, have generated a great deal of interest; however, their size

precludes efficient clearance from the circulatory and renal systems while exhibiting long-term toxicity. Several studies have demonstrated the use of infrared dye-labeled probes in optical imaging.

1. In a comparison of gamma scintigraphy and NIR imaging, a cyclopentapeptide dual-labeled with ^{111}In and an NIR fluorophore was used to image $\alpha\beta3$ -integrin positive melanoma xenografts ^[3].
2. Near-infrared labeled RGD targeting $\alpha\beta3$ -integrin has been used in numerous studies to target a variety of cancers ^[4].
3. An NIR fluorophore has been conjugated to epidermal growth factor (EGF) for imaging of tumor progression ^[5].
4. An NIR fluorophore was compared to Cy5.5, suggesting that longer-wavelength dyes may produce more effective targeting agents for optical imaging ^[6].
5. Pamidronate has been labeled with an NIR fluorophore and used as a bone imaging agent to detect osteoblastic activity in a living animal ^[7].
6. An NIR fluorophore-labeled GPI, a potent inhibitor of PSMA (prostate specific membrane antigen) ^[8].
7. Use of human serum albumin labeled with an NIR fluorophore as a tracking agent for mapping of sentinel lymph nodes ^[9].
8. 2-Deoxy-D-glucose labeled with an NIR fluorophore ^[10].

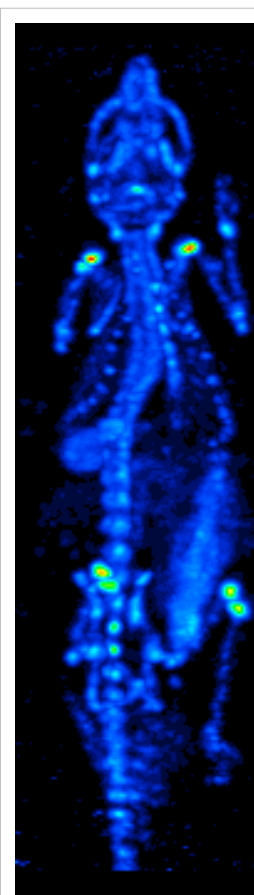
Single photon emission computed tomography (SPECT)

The main purpose of SPECT when used in brain imaging is to measure the regional cerebral blood flow (rCBF). The development of computed tomography in the 1970s allowed mapping of the distribution of the radioisotopes in the brain, and led to the technique now called SPECT.

The imaging agent used in SPECT emits gamma rays, as opposed to the positron emitters (such as ^{18}F) used in PET. There are a range of radiotracers (such as $^{99\text{m}}\text{Tc}$, ^{111}In , ^{123}I , ^{201}Tl) that can be used, depending on the specific application.

Xenon (^{133}Xe) gas is one such radiotracer. It has been shown to be valuable for diagnostic inhalation studies for the evaluation of pulmonary function; for imaging the lungs; and may also be used to assess rCBF. Detection of this gas occurs via a gamma camera—which is a scintillation detector consisting of a collimator, a NaI crystal, and a set of photomultiplier tubes.

By rotating the gamma camera around the head, a three dimensional image of the distribution of the radiotracer can be obtained by employing filtered back projection or other tomographic techniques. The radioisotopes used in SPECT have relatively long half lives (a few hours to a few days) making them easy to produce and relatively cheap. This represents the major advantage of SPECT as a brain imaging technique, since it is significantly cheaper than either PET or fMRI. However it lacks good spatial (i.e., where exactly the particle is) or temporal (i.e., did the contrast agent signal happen at this millisecond, or that millisecond) resolution. Additionally, due to the radioactivity of the contrast agent, there are safety aspects concerning the administration of radioisotopes to the subject, especially for serial studies.



SPECT image (bone tracer)
of a mouse MIP

Positron emission tomography (PET)

Positron emission tomography is a nuclear medicine imaging technique which produces a three-dimensional image or picture of functional processes in the body. The theory behind PET is simple enough. First a molecule is tagged

with a positron emitting isotope. These positrons annihilate with nearby electrons, emitting two 511,000 eV photons, directed 180 degrees apart in opposite directions. These photons are then detected by the scanner which can estimate the density of positron annihilations in a specific area. When enough interactions and annihilations have occurred, the density of the original molecule may be measured in that area. Typical isotopes include ^{11}C , ^{13}N , ^{15}O , ^{18}F , ^{64}Cu , ^{62}Cu , ^{124}I , ^{76}Br , ^{82}Rb and ^{68}Ga , with ^{18}F being the most clinically utilized. One of the major disadvantages of PET is that most of the probes must be made with a cyclotron. Most of these probes also have a half life measured in hours, forcing the cyclotron to be on site. These factors can make PET prohibitively expensive. PET imaging does have many advantages though. First and foremost is its sensitivity: a typical PET scanner can detect between 10^{-11} mol/L to 10^{-12} mol/L concentrations.

Ultrasound

Explanation of how it works basics how it would be used in imaging multiple targets.

Probes and the imaging of molecular interactions

In order to image multiple targets you must first identify and develop the interactions of which you are trying to take advantage. Developing good probes is often difficult and is an area of intense research.

See also

- Predictive medicine
- Translational medicine
- Chemical imaging
- EMMI European Master in Molecular Imaging

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Further reading

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2. Weissleder R, Mahmood U. Molecular imaging, Radiology 2001: 219:316-333
3. Piwnica-worms D, Luker KE. Imaging Protein-protein interactions in whole cells and living animals. Ernst Schering Res Found Workshop. 2005;(49):35-41.
4. Massoud TF, Gambhir SS. Molecular imaging in living subjects: seeing fundamental biological processes in a new light, Genes & Development 2003: 545-580

External links

- European Master in Molecular Imaging (<http://www.e-mmi.eu/>)
 - Society for Molecular Imaging (<http://www.molecularimaging.org/>)
 - Understanding Molecular Imaging and biomarker usage (<http://www.carestreamhealth.com/scientific-insights.html>)
 - Annual Imaging Meeting (<http://www.imagingmeeting.com/>) - Annual conference on Imaging in clinical and pre-clinical imaging
 - Molecular Imaging Research update ([http://www.reportergene.com/search/label/molecular imaging](http://www.reportergene.com/search/label/molecular+imaging)) from Reportergene
 - Molecular Imaging Center (<http://www.molecularimagingcenter.org/>)
 - Understanding Near-Infrared Imaging (http://www.licor.com/bio/products/imaging_systems/pearl/pearl_sensitivity.jsp/) - Resource to better understand the benefits of Near-Infrared imaging.
 - Society for Neuroscience (<http://www.sfn.org/>) -
 - European Society for Molecular Imaging (<http://www.e-smi.eu>) -
 - European Institute for Biomedical Imaging Research (<http://www.eibir.org>) -
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Tomography

Tomography is imaging by sections or sectioning, through the use of any kind of penetrating wave. A device used in tomography is called a **tomograph**, while the image produced is a **tomogram**. The method is used in radiology, archaeology, biology, geophysics, oceanography, materials science, astrophysics and other sciences. In most cases it is based on the mathematical procedure called **tomographic reconstruction**. The word was derived from the Greek word *tomos* which means "part" or "section", representing the idea of "a section", "a slice" or "a cutting". A tomography of several sections of the body is known as a polytomography.

Etymology

The word "tomography" is derived from the Greek *tomos* (part) and *graphein* (to write).

Description

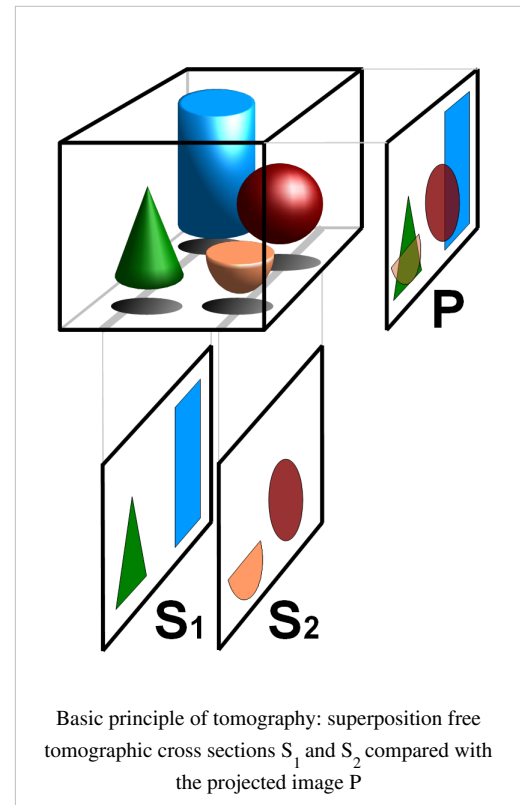
In conventional medical X-ray tomography, clinical staff make a sectional image through a body by moving an X-ray source and the film in opposite directions during the exposure. Consequently, structures in the focal plane appear sharper, while structures in other planes appear blurred.^[1] By modifying the direction and extent of the movement, operators can select different focal planes which contain the structures of interest. Before the advent of more modern computer-assisted techniques, this technique, ideated in the 1930s by the radiologist Alessandro Vallebona, proved useful in reducing the problem of superimposition of structures in projectional (shadow) radiography.

Modern tomography

More modern variations of tomography involve gathering projection data from multiple directions and feeding the data into a tomographic reconstruction software algorithm processed by a computer.^[2] Different types of signal acquisition can be used in similar calculation algorithms in order to create a tomographic image. With current 2005 technology, tomograms are derived using several different physical phenomena listed in the following table.

Physical phenomenon	Type of tomogram
X-rays	CT
gamma rays	SPECT
radio-frequency waves	MRI
electron-positron annihilation	PET
electrons	Electron tomography or 3D TEM
ions	atom probe

Some recent advances rely on using simultaneously integrated physical phenomena, e.g. X-rays for both CT and angiography, combined CT/MRI and combined CT/PET.



The term *volume imaging* might subsume these technologies more accurately than the term *tomography*. However, in the majority of cases in clinical routine, staff request output from these procedures as 2-D slice images. As more and more clinical decisions come to depend on more advanced volume visualization techniques, the terms *tomography/tomogram* may go out of fashion.

Many different reconstruction algorithms exist. Most algorithms fall into one of two categories: filtered back projection (FBP) and iterative reconstruction (IR). These procedures give inexact results: they represent a compromise between accuracy and computation time required. FBP demands fewer computational resources, while IR generally produces fewer artifacts (errors in the reconstruction) at a higher computing cost.

Although MRI and ultrasound make cross sectional images they don't acquire data from different directions. In MRI spatial information is obtained by using magnetic fields. In ultrasound, spatial information is obtained simply by focusing and aiming a pulsed ultrasound beam.

Synchrotron X-ray tomographic microscopy

Recently a new technique called synchrotron X-ray tomographic microscopy (SRXTM) allows for detailed three dimensional scanning of fossils.

Types of tomography

Name	Source of data	Abbreviation	Year of introduction
Atom probe tomography	Atom probe	APT	
Confocal microscopy (Laser scanning confocal microscopy)	Laser scanning confocal microscopy	LSCM	
Cryo-electron tomography	Cryo-electron microscopy	Cryo-ET	
Electrical capacitance tomography	Electrical capacitance	ECT	
Electrical resistivity tomography	Electrical resistivity	ERT	
Electrical impedance tomography	Electrical impedance	EIT	1984
Functional magnetic resonance imaging	Magnetic resonance	fMRI	1992
Magnetic induction tomography	Magnetic induction	MIT	
Magnetic resonance imaging or nuclear magnetic resonance tomography	Nuclear magnetic moment	MRI or MRT	
Neutron tomography	Neutron		
Ocean acoustic tomography	Sonar		
Optical coherence tomography	Interferometry	OCT	
Optical projection tomography	Optical microscope	OPT	
Photoacoustic imaging in biomedicine	Photoacoustic spectroscopy	PAT	
Positron emission tomography	Positron emission	PET	
Positron emission tomography - computed tomography	Positron emission & X-ray	PET-CT	
Quantum tomography	Quantum state		
Single photon emission computed tomography	Gamma ray	SPECT	
Seismic tomography	Ground-penetrating radar		
Thermoacoustic imaging	Photoacoustic spectroscopy	TAT	
Ultrasound-modulated optical tomography	Ultrasound	UOT	

Ultrasound transmission tomography	Ultrasound		
X-ray tomography	X-ray	CT, CATScan	1971
Zeeman-Doppler imaging	Zeeman effect		

Discrete tomography and Process tomography refer to processing techniques.

See also

- Chemical imaging
- Geophysical imaging
- Medical imaging
- MRI compared with CT
- Network tomography
- Nonogram, a type of puzzle based on a discrete model of tomography
- Radon transform
- Tomographic reconstruction

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- [2] Herman, G. T., *Fundamentals of computerized tomography: Image reconstruction from projection*, 2nd edition, Springer, 2009

External links

- International Journal of Tomography & Statistics (IJTS) (<http://www.isder.ceser.res.in/ijts.html>)
- Microtomography/Synchrotron tomography (http://www.bronnikov-algorithms.com/downloads/Andrei.Bronnikov_Image_reconstruction.pdf)

X-ray computed tomography

Computed tomography (CT) is a medical imaging method employing tomography created by computer processing.^[1] Digital geometry processing is used to generate a three-dimensional image of the inside of an object from a large series of two-dimensional X-ray images taken around a single axis of rotation.^[2]

CT produces a volume of data which can be manipulated, through a process known as "windowing", in order to demonstrate various bodily structures based on their ability to block the X-ray beam. Although historically the images generated were in the

axial or transverse plane, orthogonal to the long axis of the body, modern scanners allow this volume of data to be reformatted in various planes or even as volumetric (3D) representations of structures. Although most common in medicine, CT is also used in other fields, such as nondestructive materials testing. Another example is archaeological uses such as imaging the contents of sarcophagi or the DigiMorph project at the University of Texas at Austin which uses a CT scanner to study biological and paleontological specimens.

Usage of CT has increased dramatically over the last two decades^[3]. An estimated 72 million scans were performed in the United States in 2007.^[4]

Terminology

The word "tomography" is derived from the Greek *tomos* (slice) and *graphein* (to write). Computed tomography was originally known as the "EMI scan" as it was developed at a research branch of EMI, a company best known today for its music and recording business. It was later known as **computed axial tomography** (CAT or CT scan) and **body section röntgenography**.

Although the term "computed tomography" could be used to describe positron emission tomography and single photon emission computed tomography, in practice it usually refers to the computation of tomography from X-ray images, especially in older medical literature and smaller medical facilities.

In MeSH, "computed axial tomography" was used from 1977–79, but the current indexing explicitly includes "X-ray" in the title.^[5]



A patient is receiving a CT scan for cancer. Outside of the scanning room is an imaging computer that reveals a 3D image of the body's interior.

History

In the early 1900s, the Italian radiologist Alessandro Vallebona proposed a method to represent a single slice of the body on the radiographic film. This method was known as tomography. The idea is based on simple principles of projective geometry: moving synchronously and in opposite directions the X-ray tube and the film, which are connected together by a rod whose pivot point is the focus; the image created by the points on the focal plane appears sharper, while the images of the other points annihilate as noise. This is only marginally effective, as blurring occurs only in the "x" plane. There are also more complex devices which can move in more than one plane and perform more effective blurring.

Tomography had been one of the pillars of radiologic diagnostics until the late 1970s, when the availability of minicomputers and of the transverse axial scanning method, this last due to the work of Godfrey Hounsfield and South African-born Allan McLeod Cormack, gradually supplanted it as the modality of CT. Mathematically, the method is based upon the use of the Radon Transform invented by Johann Radon in 1917. But as Cormack remembered later^[6], he had to find the solution himself since it was only in 1972, that he learned of the work of Radon, by chance.

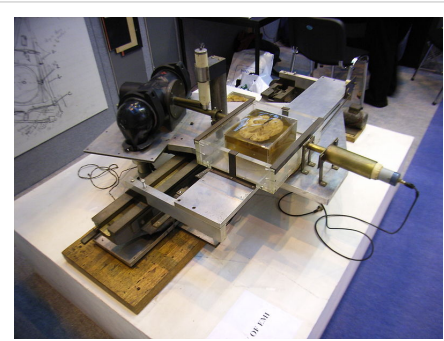
The first commercially viable CT scanner was invented by Sir Godfrey Hounsfield in Hayes, United Kingdom at EMI Central Research Laboratories using X-rays. Hounsfield conceived his idea in 1967.^[7] The first EMI-Scanner was installed at Atkinson Morley Hospital in Wimbledon, England, and the first patient brain-scan was done on 1 October 1971^[8]. It was publicly announced in 1972.

The original 1971 prototype took 160 parallel readings through 180 angles, each 1° apart, with each scan taking a little over 5 minutes. The images from these scans took 2.5 hours to be processed by algebraic reconstruction techniques on a large computer. The scanner had a single photomultiplier detector, and operated on the Translate/Rotate principle.^[8]

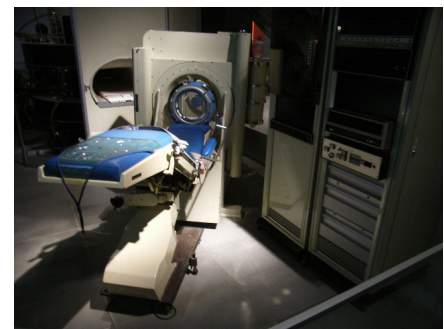
It has been claimed that thanks to the success of The Beatles, EMI could fund research and build early models for medical use.^[9] The first production X-ray CT machine (in fact called the "EMI-Scanner") was limited to making tomographic sections of the brain, but acquired the image data in about 4 minutes (scanning two adjacent slices), and the computation time (using a Data General Nova minicomputer) was about 7 minutes per picture. This scanner required the use of a water-filled Perspex tank with a pre-shaped rubber "head-cap" at the front, which enclosed the patient's head. The water-tank was used to reduce the dynamic range of the radiation reaching the detectors (between scanning outside the head compared with scanning through the bone of the skull). The images were relatively low resolution, being composed of a matrix of only 80 x 80 pixels.

In the U.S., the first installation was at the Mayo Clinic. As a tribute to the impact of this system on medical imaging the Mayo Clinic has an EMI scanner on display in the Radiology Department. Allan McLeod Cormack of Tufts University in Massachusetts independently invented a similar process, and both Hounsfield and Cormack shared the 1979 Nobel Prize in Medicine.^[10]

The first CT system that could make images of any part of the body and did not require the "water tank" was the ACTA (Automatic Computerized Transverse Axial) scanner designed by Robert S. Ledley, DDS, at Georgetown University. This machine had 30 photomultiplier tubes as detectors and completed a scan in only 9 translate/rotate cycles, much faster than the EMI-scanner. It used a DEC PDP11/34 minicomputer both to operate the



The prototype CT scanner



A historic EMI-Scanner

servo-mechanisms and to acquire and process the images. The Pfizer drug company acquired the prototype from the university, along with rights to manufacture it. Pfizer then began making copies of the prototype, calling it the "200FS" (FS meaning Fast Scan), which were selling as fast as they could make them. This unit produced images in a 256×256 matrix, with much better definition than the EMI-Scanner's 80×80.

Previous studies

A form of tomography can be performed by moving the X-ray source and detector during an exposure. Anatomy at the target level remains sharp, while structures at different levels are blurred. By varying the extent and path of motion, a variety of effects can be obtained, with variable depth of field and different degrees of blurring of "out of plane" structures.^{[11]:25}

Although largely obsolete, conventional tomography is still used in specific situations such as dental imaging (orthopantomography) or in intravenous urography.

Tomosynthesis

Digital tomosynthesis combines digital image capture and processing with simple tube/detector motion as used in conventional radiographic tomography. Although there are some similarities to CT, it is a separate technique. In CT, the source/detector makes a complete 360-degree rotation about the subject obtaining a complete set of data from which images may be reconstructed. In digital tomosynthesis, only a small rotation angle (e.g., 40 degrees) with a small number of discrete exposures (e.g., 10) are used. This incomplete set of data can be digitally processed to yield images similar to conventional tomography with a limited depth of field. However, because the image processing is digital, a series of slices at different depths and with different thicknesses can be reconstructed from the same acquisition, saving both time and radiation exposure.

Because the data acquired is incomplete, tomosynthesis is unable to offer the extremely narrow slice widths that CT offers. However, higher resolution detectors can be used, allowing very-high in-plane resolution, even if the Z-axis resolution is poor. The primary interest in tomosynthesis is in breast imaging, as an extension to mammography, where it may offer better detection rates with little extra increase in radiation exposure.

Reconstruction algorithms for tomosynthesis are significantly different from conventional CT, because the conventional filtered back projection algorithm requires a complete set of data. Iterative algorithms based upon expectation maximization are most commonly used, but are extremely computationally intensive. Some manufacturers have produced practical systems using off-the-shelf GPUs to perform the reconstruction.

Diagnostic use

Since its introduction in the 1970s, CT has become an important tool in medical imaging to supplement X-rays and medical ultrasonography. It has more recently been used for preventive medicine or screening for disease, for example CT colonography for patients with a high risk of colon cancer, or full-motion heart scans for patients with high risk of heart disease. A number of institutions offer full-body scans for the general population. However, this is a controversial practice, given its lack of proven benefit, cost, radiation exposure, and the risk of finding 'incidental' abnormalities that may trigger additional investigations.

Head

CT scanning of the head is typically used to detect infarction, tumours, calcifications, haemorrhage and bone trauma. Of the above, hypodense (dark) structures indicate infarction or tumours, hyperdense (bright) structures indicate calcifications and haemorrhage and bone trauma can be seen as disjunction in bone windows.

Chest

CT can be used for detecting both acute and chronic changes in the lung parenchyma, that is, the internals of the lungs. It is particularly relevant here because normal two dimensional x-rays do not show such defects. A variety of different techniques are used depending on the suspected abnormality. For evaluation of chronic interstitial processes (emphysema, fibrosis, and so forth), thin sections with high spatial frequency reconstructions are used—often scans are performed both in inspiration and expiration. This special technique is called High Resolution CT (HRCT). HRCT is normally done with thin section with skipped areas between the thin sections. Therefore it produces a sampling of the lung and not continuous images. Continuous images are provided in a standard CT of the chest.

For detection of airspace disease (such as pneumonia) or cancer, relatively thick sections and general purpose image reconstruction techniques may be adequate. IV contrast may also be used as it clarifies the anatomy and boundaries of the great vessels and improves assessment of the mediastinum and hilar regions for lymphadenopathy; this is particularly important for accurate assessment of cancer.

CT angiography of the chest is also becoming the primary method for detecting pulmonary embolism (PE) and aortic dissection, and requires accurately timed rapid injections of contrast (Bolus Tracking) and high-speed helical scanners. CT is the standard method of evaluating abnormalities seen on chest X-ray and of following findings of uncertain acute significance. Cardiac CTA is now being used to diagnose coronary artery disease.

According to the 2007 *New England Journal of Medicine* study, 19.2 million (31%) of the 62 million CTs done every year are for lung CTs.

Pulmonary angiogram

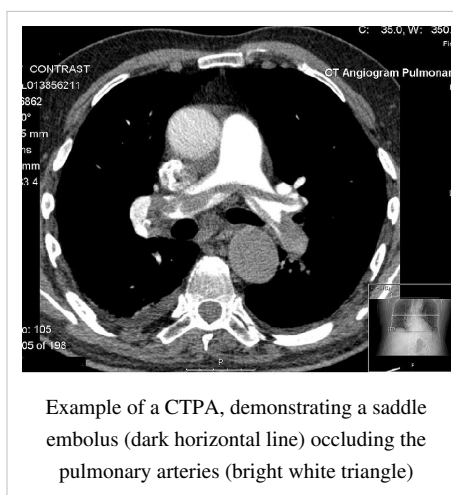
CT pulmonary angiogram (CTPA) is a medical diagnostic test used to diagnose pulmonary embolism (PE). It employs computed tomography to obtain an image of the pulmonary arteries.

It is a preferred choice of imaging in the diagnosis of PE due to its minimally invasive nature for the patient, whose only requirement for the scan is a cannula (usually a 20G).

MDCT (multi detector CT) scanners give the optimum resolution and image quality for this test. Images are usually taken on a 0.625 mm slice thickness, although 2 mm is sufficient. 50–100 mls of contrast is given to the patient at a rate of 4 ml/s. The tracker/locator is placed at the level of the pulmonary arteries, which sit roughly at the level of the carina. Images are acquired with the maximum intensity of radio-opaque contrast in the pulmonary arteries. This is done using bolus tracking.

CT machines are now so sophisticated that the test can be done with a patient visit of 5 minutes with an approximate scan time of only 5 seconds or less.

A normal CTPA scan will show the contrast filling the pulmonary vessels, looking bright white. Ideally the aorta should be empty of contrast, to reduce any partial volume artifact which may result in a false positive. Any mass filling defects, such as an embolus, will appear dark in place of the contrast, filling / blocking the space where blood



Example of a CTPA, demonstrating a saddle embolus (dark horizontal line) occluding the pulmonary arteries (bright white triangle)

should be flowing into the lungs.

Cardiac

With the advent of subsecond rotation combined with multi-slice CT (up to 320-slices), high resolution and high speed can be obtained at the same time, allowing excellent imaging of the coronary arteries (cardiac CT angiography). Images with an even higher temporal resolution can be formed using retrospective ECG gating. In this technique, each portion of the heart is imaged more than once while an ECG trace is recorded. The ECG is then used to correlate the CT data with their corresponding phases of cardiac contraction. Once this correlation is complete, all data that were recorded while the heart was in motion (systole) can be ignored and images can be made from the remaining data that happened to be acquired while the heart was at rest (diastole). In this way, individual frames in a cardiac CT investigation have a better temporal resolution than the shortest tube rotation time.

Because the heart is effectively imaged more than once (as described above), cardiac CT angiography results in a relatively high radiation exposure around 12 mSv. Currently, newer acquisition protocols have been developed drastically reducing the xRays radiation exposure, down to 1 milliSievert (cfr. Pavone, Fioranelli, Dowe: *Computed Tomography or Coronary Arteries*, Springer 2009). For the sake of comparison, a chest X-ray carries a dose of approximately $0.02^{[12]}$ to 0.2 mSv and natural background radiation exposure is around 0.01 mSv/day. Thus, cardiac CTA is equivalent to approximately 100-600 chest X-rays or over 3 years worth of natural background radiation. Methods are available to decrease this exposure, however, such as prospectively decreasing radiation output based on the concurrently acquired ECG (aka tube current modulation.) This can result in a significant decrease in radiation exposure, at the risk of compromising image quality if there is any arrhythmia during the acquisition. The significance of radiation doses in the diagnostic imaging range has not been proven, although the possibility of inducing an increased cancer risk across a population is a source of significant concern. This potential risk must be weighed against the competing risk of not performing a test and potentially not diagnosing a significant health problem such as coronary artery disease.

It is uncertain whether this modality will replace invasive coronary catheterization. Currently, it appears that the greatest utility of cardiac CT lies in ruling out coronary artery disease rather than ruling it in. This is because the test has a high sensitivity (greater than 90%) and thus a negative test result means that a patient is very unlikely to have coronary artery disease and can be worked up for other causes of their chest symptoms. This is termed a high negative predictive value. A positive result is less conclusive and often will be confirmed (and possibly treated) with subsequent invasive angiography. The positive predictive value of cardiac CTA is estimated at approximately 82% and the negative predictive value is around 93%.

Dual Source CT scanners, introduced in 2005, allow higher temporal resolution by acquiring a full CT slice in only half a rotation, thus reducing motion blurring at high heart rates and potentially allowing for shorter breath-hold time. This is particularly useful for ill patients who have difficulty holding their breath or who are unable to take heart-rate lowering medication.

The speed advantages of 64-slice MSCT have rapidly established it as the minimum standard for newly installed CT scanners intended for cardiac scanning. Manufacturers have developed 320-slice and true 'volumetric' scanners, primarily for their improved cardiac scanning performance.

The latest MSCT scanners acquire images only at 70-80% of the R-R interval (late diastole). This prospective gating can reduce effective dose from 10-15mSv to as little as 1.2mSv in follow-up patients acquiring at 75% of the R-R interval. Effective doses at a centre with well trained staff doing coronary imaging can average less than the doses for conventional coronary angiography.

Abdominal and pelvic

CT is a sensitive method for diagnosis of abdominal diseases. It is used frequently to determine stage of cancer and to follow progress. It is also a useful test to investigate acute abdominal pain (especially of the lower quadrants, whereas ultrasound is the preferred first line investigation for right upper quadrant pain). Renal stones, appendicitis, pancreatitis, diverticulitis, abdominal aortic aneurysm, and bowel obstruction are conditions that are readily diagnosed and assessed with CT. CT is also the first line for detecting solid organ injury after trauma.

Multidetector CT (MDCT) can clearly delineate anatomic structures in the abdomen, which is critical in the diagnosis of internal diaphragmatic and other nonpalpable or unsuspected hernias. MDCT also offers clear detail of the abdominal wall allowing wall hernias to be identified accurately.^[13]

Oral and/or rectal contrast may be used depending on the indications for the scan. A dilute (2% w/v) suspension of barium sulfate is most commonly used. The concentrated barium sulfate preparations used for fluoroscopy e.g. barium enema are too dense and cause severe artifacts on CT. Iodinated contrast agents may be used if barium is contraindicated (for example, suspicion of bowel injury). Other agents may be required to optimize the imaging of specific organs, such as rectally administered gas (air or carbon dioxide) or fluid (water) for a colon study, or oral water for a stomach study.

CT has limited application in the evaluation of the *pelvis*. For the female pelvis in particular, ultrasound and MRI are the imaging modalities of choice. Nevertheless, it may be part of abdominal scanning (e.g. for tumors), and has uses in assessing fractures.

CT is also used in osteoporosis studies and research alongside dual energy X-ray absorptiometry (DXA). Both CT and DXA can be used to assess bone mineral density (BMD) which is used to indicate bone strength, however CT results do not correlate exactly with DXA (the gold standard of BMD measurement). CT is far more expensive, and subjects patients to much higher levels of ionizing radiation, so it is used infrequently.

Extremities

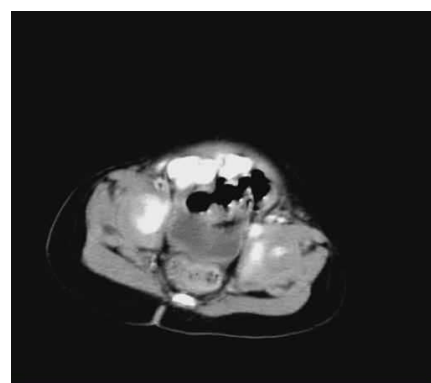
CT is often used to image complex fractures, especially ones around joints, because of its ability to reconstruct the area of interest in multiple planes. Fractures, ligamentous injuries and dislocations can easily be recognised with a 0.2 mm resolution.^{[14] [15]}

Advantages and disadvantages

Advantages over traditional radiography

There are several advantages that CT has over traditional 2D medical radiography. First, CT completely eliminates the superimposition of images of structures outside the area of interest. Second, because of the inherent high-contrast resolution of CT, differences between tissues that differ in physical density by less than 1% can be distinguished. Finally, data from a single CT imaging procedure consisting of either multiple contiguous or one helical scan can be viewed as images in the axial, coronal, or sagittal planes, depending on the diagnostic task. This is referred to as multiplanar reformatted imaging.

CT is regarded as a moderate to high radiation diagnostic technique. While technical advances have improved radiation efficiency, there has been simultaneous pressure to obtain higher-resolution imaging and use more complex



CT Scan of 11 cm **Wilms' tumor** of right kidney in 13 month old patient.

scan techniques, both of which require higher doses of radiation. The improved resolution of CT has permitted the development of new investigations, which may have advantages; compared to conventional angiography for example, CT angiography avoids the invasive insertion of an arterial catheter and guidewire; CT colonography (also known as virtual colonoscopy or VC for short) may be as useful as a barium enema for detection of tumors, but may use a lower radiation dose. CT VC is increasingly being used in the UK as a diagnostic test for bowel cancer and can negate the need for a colonoscopy.

The greatly increased availability of CT, together with its value for an increasing number of conditions, has been responsible for a large rise in popularity. So large has been this rise that, in the most recent comprehensive survey in the United Kingdom, CT scans constituted 7% of all radiologic examinations, but contributed 47% of the total collective dose from medical X-ray examinations in 2000/2001.^[16] Increased CT usage has led to an overall rise in the total amount of medical radiation used, despite reductions in other areas. In the United States and Japan for example, there were 26 and 64 CT scanners per 1 million population in 1996. In the U.S., there were about 3 million CT scans performed in 1980, compared to an estimated 62 million scans in 2006.^[17]

The radiation dose for a particular study depends on multiple factors: volume scanned, patient build, number and type of scan sequences, and desired resolution and image quality. Additionally, two helical CT scanning parameters that can be adjusted easily and that have a profound effect on radiation dose are tube current and pitch.^[18]

Computed tomography (CT) scan has been shown to be more accurate than radiographs in evaluating anterior interbody fusion but may still over-read the extent of fusion.^[19]

Safety concerns

The increased use of CT scans has been the greatest in two fields: screening of adults (screening CT of the lung in smokers, virtual colonoscopy, CT cardiac screening and whole-body CT in asymptomatic patients) and CT imaging of children. Shortening of the scanning time to around 1 second, eliminating the strict need for subject to remain still or be sedated, is one of the main reasons for large increase in the pediatric population (especially for the diagnosis of appendicitis).^[17] CT scans of children have been estimated to produce non-negligible increases in the probability of lifetime cancer mortality, leading to calls for the use of reduced current settings for CT scans of children.^[20] These calculations are based on the assumption of a linear relationship between radiation dose and cancer risk; this claim is controversial, as some but not all evidence shows that smaller radiation doses are not harmful.^[17] Estimated lifetime cancer mortality risks attributable to the radiation exposure from a CT in a 1-year-old are 0.18% (abdominal) and 0.07% (head)—an order of magnitude higher than for adults—although those figures still represent a small increase in cancer mortality over the background rate. In the United States, of approximately 600,000 abdominal and head CT examinations annually performed in children under the age of 15 years, a rough estimate is that 500 of these individuals might ultimately die from cancer attributable to the CT radiation.^[21] The additional risk is still very low (0.35%) compared to the background risk of dying from cancer (23%).^[21] However, if these statistics are extrapolated to the current number of CT scans, the additional rise in cancer mortality could be 1.5 to 2%. Furthermore, certain conditions can require children to be exposed to multiple CT scans. Again, these calculations can be problematic because the assumptions underlying them could overestimate the risk.^[17]

In 2009 a number of studies appeared that further defined the risk of cancer that may be caused by CT scans.^[22] One study indicated that radiation by CT scans is often higher and more variable than cited and each of the 19,500 CT scans that are daily performed in the US is equivalent to 30 to 442 chest x-rays in radiation. It has been estimated that CT radiation exposure will result in 29,000 new cancer cases just from the CT scans performed in 2007.^[22] The most common cancers caused by CT are thought to be lung cancer, colon cancer and leukemia with younger people and women more at risk. These conclusions, however, are criticized by the American College of Radiology (ACR) that maintains that the life expectancy of CT scanned patients is not that of the general population and that the model of calculating cancer is based on total body radiation exposure and thus faulty.^[22]

CT scans can be performed with different settings for lower exposure in children, although these techniques are often not employed. Surveys have suggested that currently, many CT scans are performed unnecessarily. Ultrasound scanning or magnetic resonance imaging are alternatives (for example, in appendicitis or brain imaging) without the risk of radiation exposure. Although CT scans come with an additional risk of cancer (it can be estimated that the radiation exposure from a full body scan is the same as standing 2.4 km away from the WWII atomic bomb blasts in Japan^{[23] [24]}), especially in children, the benefits that stem from their use outweighs the risk in many cases.^[21] Studies support informing parents of the risks of pediatric CT scanning.^[25]

Typical scan doses

Examination	Typical effective dose (mSv)	(millirem)
Chest X-ray	0.1	10
Head CT	1.5 ^[26]	150
Screening mammography	3 ^[17]	300
Abdomen CT	5.3 ^[26]	530
Chest CT	5.8 ^[26]	580
CT colonography (virtual colonoscopy)	3.6–8.8	360–880
Chest, abdomen and pelvis CT	9.9 ^[26]	990
Cardiac CT angiogram	6.7–13 ^[27]	670–1300
Barium enema	15 ^[17]	1500
Neonatal abdominal CT	20 ^[17]	2000

For purposes of comparison, the average background exposure in the UK is 1-3 mSv per year.

Adverse reactions to contrast agents

Because contrast CT scans rely on intravenously administered contrast agents in order to provide superior image quality, there is a low but non-negligible level of risk associated with the contrast agents themselves. Many patients report nausea and discomfort, including warmth in the crotch which mimics the sensation of wetting oneself. Certain patients may experience severe and potentially life-threatening allergic reactions to the contrast dye.

The contrast agent may also induce kidney damage. The risk of this is increased with patients who have preexisting renal insufficiency, preexisting diabetes, or reduced intravascular volume. In general, if a patient has normal kidney function, then the risks of contrast nephropathy are negligible. Patients with mild kidney impairment are usually advised to ensure full hydration for several hours before and after the injection. For moderate kidney failure, the use of iodinated contrast should be avoided; this may mean using an alternative technique instead of CT, e.g., MRI. Paradoxically, patients with severe renal failure requiring dialysis do not require special precautions, as their kidneys have so little function remaining that any further damage would not be noticeable and the dialysis will remove the contrast agent.

Low-dose CT scan

An important issue within radiology today is how to reduce the radiation dose during CT examinations without compromising the image quality. Generally, higher radiation doses result in higher-resolution images, while lower doses lead to increased image noise and unsharp images. Increased dosage raises the risk of radiation induced cancer — a four-phase abdominal CT gives the same radiation dose as 300 chest x-rays. Several methods exist which can reduce the exposure to ionizing radiation during a CT scan.

1. New software technology can significantly reduce the required radiation dose. The software works as a filter that reduces random noise and enhances structures. In this way, it is possible to get high-quality images and at the same time lower the dose by as much as 30 to 70 percent.
2. Individualize the examination and adjust the radiation dose to the body type and body organ examined. Different body types and organs require different amounts of radiation.
3. Prior to every CT examination, evaluate the appropriateness of the exam whether it is motivated or if another type of examination is more suitable. Higher resolution is not always suitable for any given scenario, such as detection of small pulmonary masses^[28]

Computed tomography versus MRI

The basic mathematics of the 2D-Fourier transform in CT reconstruction is very similar to the 2D-FT NMRI, but the computer data processing in CT does differ in detail, as for example in the case of the volume rendering and artifact elimination algorithms that are specific to CT.

Prevalence

Usage of CT has increased dramatically over the last two decades^[29]. An estimated 72 million scans were performed in the United States in 2007.^[30] In Calgary Canada 12.1% of people who present to the emergency with an urgent complaint received a CT scan, most commonly either of the head or the abdomen. The percentage who received CT however varied markedly by the emergency physician who saw them from 1.8% to 25%.^[31]

Process

X-ray slice data is generated using an X-ray source that rotates around the object; X-ray sensors are positioned on the opposite side of the circle from the X-ray source. The earliest sensors were scintillation detectors, with photomultiplier tubes excited by (typically) cesium iodide crystals. Cesium iodide was replaced during the 1980s by ion chambers containing high pressure Xenon gas. These systems were in turn replaced by scintillation systems based on photo diodes instead of photomultipliers and modern scintillation materials with more desirable characteristics. Many data scans are progressively taken as the object is gradually passed through the gantry.

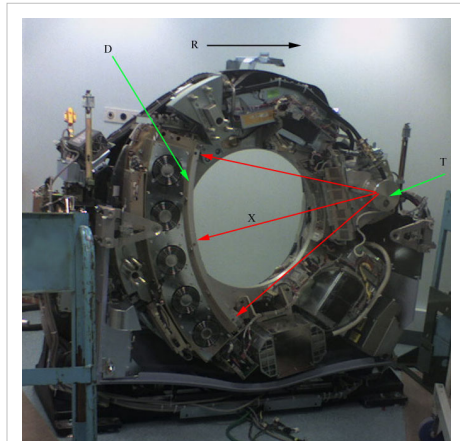
Newer machines with faster computer systems and newer software strategies can process not only individual cross sections but continuously changing cross sections as the gantry, with the object to be imaged, is slowly and smoothly slid through the X-ray circle. These are called *helical* or *spiral CT* machines. Their computer systems integrate the data of the moving individual slices to generate three dimensional volumetric information (3D-CT scan), in turn viewable from multiple different perspectives on attached CT workstation monitors. This type of data acquisition requires enormous processing power, as the data are arriving in a continuous stream and must be processed in real-time.

In conventional CT machines, an X-ray tube and detector are physically rotated behind a circular shroud (see the image above right); in the electron beam tomography (EBT) the tube is far larger and higher power to support the high temporal resolution. The electron beam is deflected in a hollow funnel-shaped vacuum chamber. X-rays are generated when the beam hits the stationary target. The detector is also stationary. This arrangement can result in very fast scans, but is extremely expensive.

CT is used in medicine as a diagnostic tool and as a guide for interventional procedures. Sometimes contrast materials such as intravenous iodinated contrast are used. This is useful to highlight structures such as blood vessels that otherwise would be difficult to delineate from their surroundings. Using contrast material can also help to obtain functional information about tissues.

Once the scan data has been acquired, the data must be processed using a form of tomographic reconstruction, which produces a series of cross-sectional images. The most common technique in general use is filtered back projection, which is straight-forward to implement and can be computed rapidly. Mathematically, this method is based on the Radon transform. However, this is not the only technique available: the original EMI scanner solved the tomographic reconstruction problem by linear algebra, but this approach was limited by its high computational complexity, especially given the computer technology available at the time. More recently, manufacturers have developed iterative physical model-based expectation-maximization techniques. These techniques are advantageous because they use an internal model of the scanner's physical properties and of the physical laws of X-ray interactions. By contrast, earlier methods have assumed a perfect scanner and highly simplified physics, which leads to a number of artefacts and reduced resolution - the result is images with improved resolution, reduced noise and fewer artefacts, as well as the ability to greatly reduce the radiation dose in certain circumstances. The disadvantage is a very high computational requirement, which is at the limits of practicality for current scan protocols.

Pixels in an image obtained by CT scanning are displayed in terms of relative radiodensity. The pixel itself is displayed according to the mean attenuation of the tissue(s) that it corresponds to on a scale from +3071 (most attenuating) to -1024 (least attenuating) on the Hounsfield scale. Pixel is a two dimensional unit based on the matrix size and the field of view. When the CT slice thickness is also factored in, the unit is known as a Voxel, which is a three dimensional unit. The phenomenon that one part of the detector cannot differentiate between different tissues is called the "*Partial Volume Effect*". That means that a big amount of cartilage and a thin layer of compact bone can cause the same attenuation in a voxel as hyperdense cartilage alone. Water has an attenuation of 0 Hounsfield units (HU) while air is -1000 HU, cancellous bone is typically +400 HU, cranial bone can reach 2000 HU or more (os temporale) and can cause artifacts. The attenuation of metallic implants depends on atomic number of the element used: Titanium usually has an amount of +1000 HU, iron steel can completely extinguish the X-ray and is therefore responsible for well-known line-artifacts in computed tomograms. Artifacts are caused by abrupt transitions between low- and high-density materials, which results in data values that exceed the dynamic range of the processing electronics.



CT scanner with cover removed to show the principle of operation

Artifacts

Although CT is a relatively accurate test, it is liable to produce artifacts, such as the following:^[2], Chapters 3 and 5

- **Aliasing artifact or streaks**

These appear as dark lines which radiate away from sharp corners. It occurs because it is impossible for the scanner to "sample" or take enough projections of the object, which is usually metallic. It can also occur when an insufficient X-ray tube current is selected, and insufficient penetration of the x-ray occurs. These artifacts are also closely tied to motion during a scan. This type of artifact commonly occurs in head images around the pituitary fossa area.

- **Partial volume effect**

This appears as "blurring" over sharp edges. It is due to the scanner being unable to differentiate between a small amount of high-density material (e.g. bone) and a larger amount of lower density (e.g., cartilage). The processor tries to average out the two densities or structures, and information is lost. This can be partially overcome by scanning using thinner slices.

- **Ring artifact**

Probably the most common mechanical artifact, the image of one or many "rings" appears within an image. This is usually due to a detector fault.

- **Noise artifact**

This appears as graining on the image and is caused by a low signal to noise ratio. This occurs more commonly when a thin slice thickness is used. It can also occur when the power supplied to the X-ray tube is insufficient to penetrate the anatomy.

- **Motion artifact**

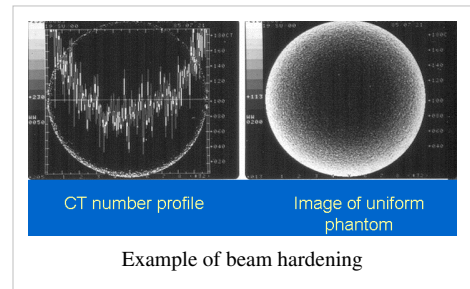
This is seen as blurring and/or streaking which is caused by movement of the object being imaged.

- **Windmill**

Streaking appearances can occur when the detectors intersect the reconstruction plane. This can be reduced with filters or a reduction in pitch.

- **Beam hardening**

This can give a "cupped appearance". It occurs when there is more attenuation in the center of the object than around the edge. This is easily corrected by filtration and software.



Three-dimensional (3D) image reconstruction

The principle

Because contemporary CT scanners offer isotropic or near isotropic, resolution, display of images does not need to be restricted to the conventional axial images. Instead, it is possible for a software program to build a volume by "stacking" the individual slices one on top of the other. The program may then display the volume in an alternative manner.^[32]

Multiplanar reconstruction

Multiplanar reconstruction (MPR) is the simplest method of reconstruction. A volume is built by stacking the axial slices. The software then cuts slices through the volume in a different plane (usually orthogonal). Optionally, a special projection method, such as maximum-intensity projection (MIP) or minimum-intensity projection (mIP), can be used to build the reconstructed slices.

MPR is frequently used for examining the spine. Axial images through the spine will only show one vertebral body at a time and cannot reliably show the intervertebral discs. By reformatting the volume, it becomes much easier to visualise the position of one vertebral body in relation to the others.

Modern software allows reconstruction in non-orthogonal (oblique) planes so that the optimal plane can be chosen to display an anatomical structure. This may be particularly useful for visualising the structure of the bronchi as these do not lie orthogonal to the direction of the scan.

For vascular imaging, curved-plane reconstruction can be performed. This allows bends in a vessel to be "straightened" so that the entire length can be visualised on one image, or a short series of images. Once a vessel has been "straightened" in this way, quantitative measurements of length and cross sectional area can be made, so that surgery or interventional treatment can be planned.

MIP reconstructions enhance areas of high radiodensity, and so are useful for angiographic studies. mIP reconstructions tend to enhance air spaces so are useful for assessing lung structure.

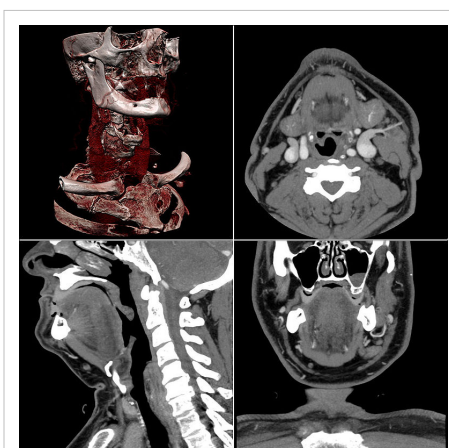
3D rendering techniques

Surface rendering

A threshold value of radiodensity is set by the operator (e.g. a level that corresponds to bone). From this, a three-dimensional model can be constructed using edge detection image processing algorithms and displayed on screen. Multiple models can be constructed from various different thresholds, allowing different colors to represent each anatomical component such as bone, muscle, and cartilage. However, the interior structure of each element is not visible in this mode of operation.

Volume rendering

Surface rendering is limited in that it will only display surfaces which meet a threshold density, and will only display the surface that is closest to the imaginary viewer. In volume rendering, transparency and colors are used to allow a better representation of the volume to be shown in a single image—e.g. the bones of the pelvis could be displayed as semi-transparent, so that even at an oblique angle, one part of the image does not conceal another.



Typical screen layout for diagnostic software, showing one 3D and three MPR views

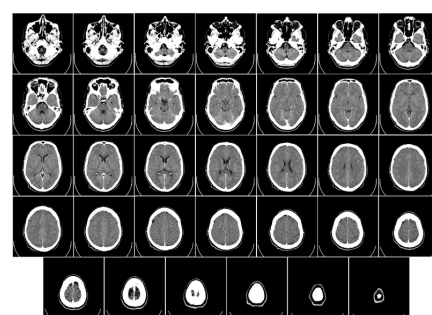
Image segmentation

Where different structures have similar radiodensity, it can become impossible to separate them simply by adjusting volume rendering parameters. The solution is called segmentation, a manual or automatic procedure that can remove the unwanted structures from the image.

Example

Some slices of a cranial CT scan are shown below. The bones are whiter than the surrounding area. (Whiter means higher attenuation.) Note the blood vessels (arrowed) showing brightly due to the injection of an iodine-based contrast agent.

A volume rendering of this volume clearly shows the high density bones.



Computed tomography of human brain, from base of the skull to top. Taken with intravenous contrast medium.

After using a segmentation tool to remove the bone, the previously concealed vessels can now be demonstrated.



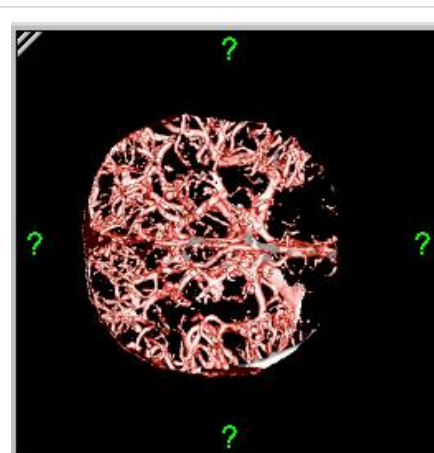
Bone reconstructed in 3D

Industrial Computed Tomography

Industrial CT Scanning (Industrial Computed Tomography) is a process which utilizes x-ray equipment to produce 3D representations of components both externally and internally. Industrial CT scanning has been utilized in many areas of industry for internal inspection of components. Some of the key uses for CT scanning have been flaw detection, failure analysis, metrology, assembly analysis and reverse engineering applications

See also

- Virtopsy
- Xenon-enhanced CT scanning
- X-ray microtomography



Brain vessels reconstructed in 3D after bone has been removed by segmentation

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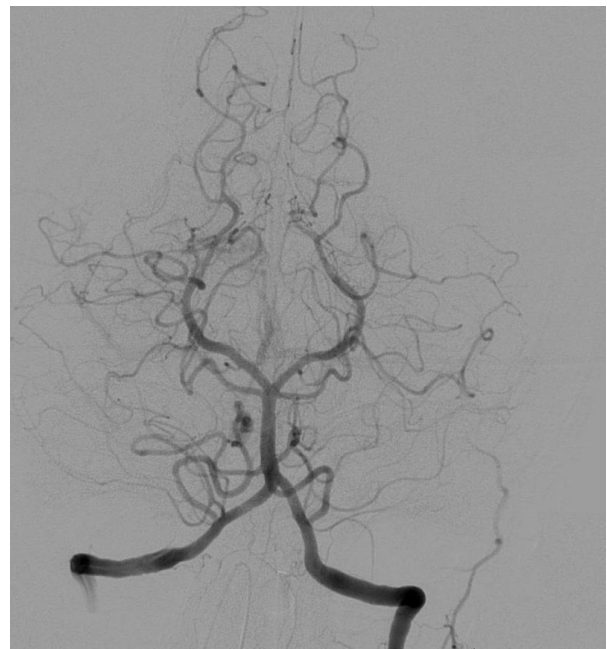
External links

- Open-source computed tomography simulator with educational tracing displays (<http://ctsimg.org>)
- idoimaging.com: Free software for viewing CT and other medical imaging files (<http://www.idoimaging.com>)
- CT Artefacts (<http://www.impactscan.org/slides/impactcourse/artefacts/img0.html>) by David Platten
- DigiMorph (<http://digimorph.org/>) A library of 3D imagery based on CT scans of the internal and external structure of living and extinct plants and animals.
- MicroCT and calcified tissues (http://www.med.univ-angers.fr/discipline/lab_histo/page_microCT.htm) A website dedicated to microCT in the microscopic analysis of calcified tissues.
- Free Radiology Resource for Radiologists, Radiographers, and Technical Assistance (<http://www.mdct.com.au>.)
- Radiation Risk Calculator (<http://www.xrayrisk.com>) Calculate cancer risk from CT scans and xrays.
- CT scanner video - gantry (<http://www.radrounds.com/video/ct-scanner-gantry-full-speed>)
- CT in your clinical practice (<http://www.ajronline.org/cgi/data/183/3/DC1/1>) by Gregory J. Kohs and Joel Legunn.
- Coronary CT angiography by Eugene Lin (<http://emedicine.medscape.com/article/1603072-overview>)
- CT physics lecture (http://www.radiolopolis.com/index.php/radiology-videos/video-gallery.html?task=viewvideo&video_id=122) excellent video lectures about physics in computed tomography
- Video documentary of patient getting a CT Scan (http://www.rosiescancerfund.com/videos/view/rosies-ct-scan_67.html)

Angiography

Angiography or **arteriography** is a medical imaging technique used to visualize the inside, or lumen, of blood vessels and organs of the body, with particular interest in the arteries, veins and the heart chambers. This is traditionally done by injecting a radio-opaque contrast agent into the blood vessel and imaging using X-ray based techniques such as fluoroscopy. The word itself comes from the Greek words *angeion*, "vessel", and *graphein*, "to write or record". The film or image of the blood vessels is called an *angiograph*, or more commonly, an *angiogram*.

The term *angiography* is strictly defined as based on projectional radiography; however, the term has been applied to newer vascular imaging techniques such as CT angiography and MR angiography. The term *isotope angiography* has also been used, although this more correctly is referred to as isotope perfusion scanning.



Angiogram showing a transverse projection of the vertebrobasilar and posterior cerebral circulation.

History

The technique was first developed in 1927 by the Portuguese physician and neurologist Egas Moniz to provide contrasted x-ray cerebral angiography in order to diagnose several kinds of nervous diseases, such as tumors, coronary heart disease and arteriovenous malformations. He is usually recognized as one of the pioneers in this field. Moniz performed the first cerebral angiogram in Lisbon in 1927, and Reynaldo Cid dos Santos performed the first aortogram in the same city in 1929. With the introduction of the Seldinger technique in 1953, the procedure became markedly safer as no sharp tools introductory devices needed to remain inside the vascular lumen.

Technique

Depending on the type of angiogram, access to the blood vessels is gained most commonly through the femoral artery, to look at the left side of the heart and the arterial system or the jugular or femoral vein, to look at the right side of the heart and the venous system. Using a system of guide wires and catheters, a type of contrast agent (which shows up by absorbing the x-rays), is added to the blood to make it visible on the x-ray images.

The X-ray images taken may either be still images, displayed on a image intensifier or film, or motion images. For all structures except the heart, the images are usually taken using a technique called digital subtraction angiography (DSA). Images in this case are usually taken at 2 - 3 frames per second, which allows the radiologist to evaluate the flow of the blood through a vessel or vessels. This technique "subtracts" the bones and other organs so only the vessels filled with contrast agent can be seen. The heart images are taken at 15-30 frames per second, not using a subtraction technique. Because DSA requires the patient to remain motionless, it cannot be used on the heart. Both these techniques enable the radiologist or cardiologist to see stenosis (blockages or narrowings) inside the vessel which may be inhibiting the flow of blood and causing pain.



angiograph

Extensions

Color (DSA)

Color (DSA) - provides a dynamic flow evaluation, greater understanding of the contrast flow within the pathology. Assists the clinician in planning of surgical procedures, and clearly demonstrate post-procedural results.

3D-DSA

3D Angiography - provides the radiologist with a 3D view of vascular structures. 3D view - helps determine spatial layout vascular structures and simplifies planning of surgical procedures.

Uses

Coronary Angiography

One of most common angiograms performed is to visualize the blood in the coronary arteries. A long, thin, flexible tube called a catheter is used to administer the x-ray contrast agent at the desired area to be visualized. The catheter is threaded into an artery in the forearm, and the tip is advanced through the arterial system into the major coronary artery. X-ray images of the transient radiocontrast distribution within the blood flowing within the coronary arteries allows visualization of the size of the artery openings. Presence or absence of atherosclerosis or atheroma within the walls of the arteries cannot be clearly determined. See coronary catheterization for more detail..

Microangiography

[Microangiography] is commonly used to visualize tiny blood vessels.

Neuro-vascular angiography

Another increasingly common angiographic procedure is neuro-vascular digital subtraction angiography in order to visualise the arterial and venous supply to the brain. Intervention work such as coil-embolisation of aneurysms and AVM gluing can also be performed.

Peripheral Angiography

Angiography is also commonly performed to identify vessel narrowing in patients with leg claudication or *cramps*, caused by reduced blood flow down the legs and to the feet; in patients with renal stenosis (which commonly causes high blood pressure) and can be used in the head to find and repair stroke. These are all done routinely through the femoral artery, but can also be performed through the brachial or axillary (arm) artery. Any stenoses found may be treated by the use of atherectomy.

Other

Other angiographic uses include the diagnosis of retinal vascular disorders, such as diabetic retinopathy and macular degeneration.

Complications

Coronary Angiography

Coronary angiographys are common and major complications are rare. These include Cardiac arrhythmias, kidney damage, blood clots (which can cause heart attack or stroke), hypotension and pericardial effusion. Minor complications can include bleeding or bruising at the site where the contrast is injected, blood vessel damage on the route to the heart from the catheter (rare) and allergic reaction to the contrast.^[1]

Cerebral Angiography

Major complications in Cerebral Angiography are also rare but include stroke, an allergic reaction to the anaesthetic other medication or the contrast medium, blockage or damage to one of the access veins in the leg, or thrombosis and embolism formation. Bleeding or bruising at the site where the contrast is injected are minor complications, delayed bleeding can also occur but is rare.^[1]

See also

- Cardiac catheterization
 - Computed Tomography Angiography
 - Contrast Medium
 - Echocardiogram
 - Electrocardiogram
 - Image intensifier
 - Intravenous digital subtraction angiography
 - Peripheral artery occlusive disease
-

External links

- MDCT^[2] - The radiology information resource for Cardiologists, Radiologists, Cardiac and Radiologic Techs - A Free Resource For Cardiac Imaging
- RadiologyInfo^[3] - The radiology information resource for patients: Angiography procedures
- Cardiac Catheterization^[4] from Angioplasty.Org
- Angiography Equipment^[5] from Siemens Medical
- Cardiovascular and Interventional Radiological Society of Europe^[6]
- [7] Coronary CT angiography by Eugene Lin

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- [3] <http://radiologyinfo.org/en/sitemap/modal-alias.cfm?modal=Angio>
- [4] <http://www.ptca.org/imaging/cath.html>
- [5] <http://www.medical.siemens.com/webapp/wcs/stores/servlet/CategoryDisplay?categoryId=12751&langId=-1&catalogId=-1&storeId=10001&catTree=100001,12764,12751&overviewId=12751&userViewId=12813&parentName=Angiography&level=0>
- [6] <http://www.cirse.org/index.php?pid=85>
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Coronary catheterization

A **coronary catheterization** is a minimally invasive procedure to access the coronary circulation and blood filled chambers of the heart using a catheter. It is performed for both diagnostic and interventional (treatment) purposes.

Coronary catheterization is one of the several cardiology diagnostic tests and procedures. Specifically, coronary catheterization is a visually interpreted test performed to recognize occlusion, stenosis, restenosis, thrombosis or aneurysmal enlargement of the coronary artery lumens; heart chamber size; heart muscle contraction performance; and some aspects of heart valve function. Important internal heart and lung blood pressures, not measurable from outside the body, can be accurately measured during the test. The relevant problems that the test deals with most commonly occur as a result of advanced

atherosclerosis -- atheroma activity within the wall of the coronary arteries. Less frequently, valvular, heart muscle, or arrhythmia issues are the primary focus of the test.



A coronary angiogram (an X-ray with radio-opaque contrast in the coronary arteries) that shows the left coronary circulation. The distal left main coronary artery (LMCA) is in the left upper quadrant of the image. Its main branches (also visible) are the left circumflex artery (LCX), which courses top-to-bottom initially and then toward the centre/bottom, and the left anterior descending (LAD) artery, which courses from left-to-right on the image and then courses down the middle of the image to project underneath of the distal LCX. The LAD, as is usual, has two large diagonal branches, which arise at the centre-top of the image and course toward the centre/right of the image.

Coronary artery luminal narrowing reduces the flow reserve for oxygenated blood to the heart, typically producing intermittent angina. Very advanced luminal occlusion usually produces a heart attack. However, it has been increasingly recognized, since the late 1980s, that coronary catheterization does not allow the recognition of the presence or absence of coronary atherosclerosis itself, only significant luminal changes which have occurred as a result of end stage complications of the atherosclerotic process. See IVUS and atheroma for a better understanding of this issue.

History

The technique of angiography was first developed in 1927 by the Portuguese physician Egas Moniz to provide contrasted x-ray in order to diagnose nervous diseases, such as tumors, coronary heart disease and arteriovenous malformations. He is recognized as one of the pioneers in this field.

Coronary catheterization was further explored in 1929 when the German physician Werner Forssmann inserted a plastic tube in his cubital vein and guided it to the right chamber of the heart. He took an x-ray to prove his success and published it on November 5 1929 with the title "Über die Sondierung des rechten Herzens" (About probing of the right heart). The coronarography of the left heart was introduced in 1953 with the report by a Portuguese group, published in *Cardiologia*, *International Archives of Cardiology* volume 22, pages 45-61, by E. Coelho et al., entitled *L'artériographie des coronaires chez l'homme vivant*. They were the first to inject radiocontrast in the coronary arteries. In 1954 George C. Willis injected the coronary arteries with contrast medium in order to monitor the reversal of coronary artery disease after proving to his own satisfaction, that Guinea pigs suffered from the same scurvy related coronary atherosclerosis as humans lacking vitamin C. He successfully demonstrated reversal of coronary artery disease or its arrestation in 70% of his sample in the St. Anne's and Queen Mary VA hospitals of Montreal. His paper "Serial arteriography in atherosclerosis" (G.C. Willis, A.W. Light, W.S. Cow. *Canadian Med. Assn. J.* Dec. 1954. Vol 71 Pp. 562-568) is the definitive first report of success in reversing the human disease with vitamin C rendering the later development of the coronary bypass unnecessary. In 1960 F. Mason Sones, a pediatric cardiologist at the Cleveland Clinic, accidentally injected radiocontrast in a coronary artery instead of the left ventricle. Although the patient had a reversible cardiac arrest, Sones and Shirey developed the procedure further, and are credited with the discovery (Connolly 2002); they published a series of 1,000 patients in 1966 (Proudfit *et al.*).

Since the late 1970s, building on the pioneering work of Charles Dotter in 1964 and especially Andreas Gruentzig starting in 1977, coronary catheterization has been extended to therapeutic uses: (a) the performance of less invasive physical treatment for angina and some of the complications of severe atherosclerosis, (b) treating heart attacks before complete damage has occurred and (c) research for better understanding of the pathology of coronary artery disease and atherosclerosis. Today, and more ethically utilising the definitive work of Michelson, Morganroth, Nichols and MacVaugh (*Arch Intern Med.* 1979 Oct;139(10):1139-41) who established the closest possible relationship between coronary and retinal atherosclerosis, it might be judged more prudent to determine, using the fundus CardioRetinometry of Bush, whether or not and how quickly arterial disease can be reversed, before embarking on cardio-thoracic surgery.

In the early 1960s, cardiac catheterization frequently took several hours and involved significant complications for as many as 2–3% of patients. With multiple incremental improvements over time, simple coronary catheterization examinations are now commonly done more rapidly and with significantly improved outcomes.

Patient participation

The patient being examined or treated is usually awake during coronary catheterization, ideally with only local anaesthesia such as lidocaine and minimal general sedation, throughout the procedure. Performing the procedure with the patient awake is safer as the patient can immediately report any discomfort or problems and thereby facilitate rapid correction of any undesirable events. Medical monitors fail to give a comprehensive view of the patient's immediate well-being; how the patient feels is often a most reliable indicator of procedural safety.

Death, myocardial infarction, stroke, serious ventricular arrhythmia, and major vascular complications each occur in less than 1% of patients undergoing catheterization.^[1] However, though the imaging portion of the examination is often brief, because of setup and safety issues the patient is often in the lab for 20–45 minutes. Any of multiple technical difficulties, while not endangering the patient (indeed added to protect the patient's interests) can significantly increase the examination time.

Equipment

Coronary catheterization is performed in a cardiac catheterization lab, usually located within a hospital. With current designs, the patient must lay relatively flat on a narrow, minimally padded, radiolucent (transparent to X-ray) table. The X-Ray source and imaging camera equipment are on opposite sides of the patient's chest and freely move, under motorized control, around the patient's chest so images can be taken quickly from multiple angles. More advanced equipment, termed a bi-plane cath lab, uses two sets of X-Ray source and imaging cameras, each free to move independently, which allows two sets of images to be taken with each injection of radiocontrast agent.

The equipment and installation setup to perform such testing typically represents a capital expenditure of US\$2–5 million (2004), sometimes more, partially repeated every few years.

Diagnostic procedures

During coronary catheterization (often referred to as a **cath** by physicians), blood pressures are recorded and X-Ray motion picture shadow-grams of the blood inside the coronary arteries are recorded. In order to create the X-ray pictures, a physician guides a small tube-like device called a catheter, typically ~2.0 mm (6-French) in diameter, through the large arteries of the body until the tip is just within the opening of one of the coronary arteries. By design, the catheter is smaller than the lumen of the artery it is placed in; internal/intraarterial blood pressures are monitored through the catheter to verify that the catheter does not block blood flow.

The catheter is itself designed to be radiodense for visibility and it allows a clear, watery, blood compatible radiocontrast agent, commonly called an X-ray dye, to be selectively injected and mixed with the blood flowing within the artery. Typically 3–8 cc of the radiocontrast agent is injected for each image to make the blood flow visible for about 3–5 seconds as the radiocontrast agent is rapidly washed away into the coronary capillaries and then coronary veins. Without the X-ray dye injection, the blood and surrounding heart tissues appear, on X-ray, as only a mildly-shape-changing, otherwise uniform water density mass; no details of the blood and internal organ structure are discernible. The radiocontrast within the blood allows visualization of the blood flow within the arteries or heart chambers, depending on where it is injected.

If atheroma, or clots, are protruding into the lumen, producing narrowing, the narrowing may be seen instead as increased haziness within the X-ray shadow images of the blood/dye column within that portion of the artery; this is as compared to adjacent, presumed healthier, less stenotic areas. See the single frame illustration of an coronary angiogram image on the angioplasty page.

For guidance regarding catheter positions during the examination, the physician mostly relies on detailed knowledge of internal anatomy, guide wire and catheter behavior and intermittently, briefly uses fluoroscopy and a low X-ray dose to visualize when needed. This is done without saving recordings of these brief looks. When the physician is ready to record diagnostic views, which are saved and can be more carefully scrutinized later, he activates the

equipment to apply a significantly higher X-ray dose, termed cine, in order to create better quality motion picture images, having sharper radiodensity contrast, typically at 30 frames per second. The physician controls both the contrast injection, fluoroscopy and cine application timing so as to minimize the total amount of radiocontrast injected and times the X-Ray to the injection so as to minimize the total amount of X-ray used. Doses of radiocontrast agents and X-ray exposure times are routinely recorded in an effort to maximize safety.

Though not the focus of the test, calcification within the artery walls, located in the outer edges of atheroma within the artery walls, is sometimes recognizable on fluoroscopy (without contrast injection) as radiodense halo rings partially encircling, and separated from the blood filled lumen by the interceding radiolucent atheroma tissue and endothelial lining. Calcification, even though usually present, is usually only visible when quite advanced and calcified sections of the artery wall happen to be viewed on end tangentially through multiple rings of calcification, so as to create enough radiodensity to be visible on fluoroscopy.

Therapeutic procedures

By changing the diagnostic catheter to a guiding catheter, physicians can also pass a variety of instruments through the catheter and into the artery to a lesion site. The most commonly used are 0.014-inch-diameter (0.36 mm) guide wires and the balloon dilation catheters.

By injecting radiocontrast agent through a tiny passage extending down the balloon catheter and into the balloon, the balloon is progressively expanded. The hydraulic pressures are chosen and applied by the physician, according to how the balloon within the stenosis responds. The radiocontrast filled balloon is watched under fluoroscopy (it typically assumes a "dog bone" shape imposed on the outside of the balloon by the stenosis as the balloon is expanded), as it opens. As much hydraulic brute force is applied as judged needed and visualized to be effective to make the stenosis of the artery lumen visibly enlarge.

Typical normal coronary artery pressures are in the <200 mmHg range (27 kPa). The hydraulic pressures applied within the balloon may extend to as high as 19000 mmHg (2,500 kPa). Prevention of over-enlargement is achieved by choosing balloons manufactured out of high tensile strength clear plastic membranes. The balloon is initially folded around the catheter, near the tip, to create a small cross-sectional profile to facilitate passage through luminal stenotic areas and designed to inflate to a specific pre-designed diameter. If over inflated, the balloon material simply tears and allows the inflating radiocontrast agent to simply escape into the blood.

Additionally, several other devices can be advanced into the artery via a guiding catheter. These include laser catheters, stent catheters, IVUS catheters, Doppler catheter, pressure or temperature measurement catheter and various clot and grinding or removal devices. Most of these devices have turned out to be niche devices, only useful in a small percentage of situations or for research.

Stents, which are specially manufactured expandable stainless steel mesh tubes, mounted on a balloon catheter, are the most commonly used device beyond the balloon catheter. When the stent/balloon device positioned within the stenosis, the balloon is inflated which, in turn, expands the stent and the artery. The balloon is removed and the stent remains in place, supporting the inner artery walls in the more open, dilated position. Current stents generally cost around \$1,000 to 3,000 each (US 2004 dollars), the drug coated ones being the more expensive.

Advances in catheter based physical treatments

Interventional procedures have been plagued by restenosis due to the formation of endothelial tissue overgrowth at the lesion site. Restenosis is the body's response to the injury of the vessel wall from angioplasty and to the stent as a foreign body. As assessed in clinical trials during the late 1980 and 1990s, using only balloon angioplasty (POBA, plain old balloon angioplasty), up to 50% of patients suffered significant restenosis but that percentage has dropped to the single to lower two digit range with the introduction of drug-eluting stents. Sirolimus, paclitaxel and everolimus are the three drugs used in coatings which are currently FDA approved in the United States. As opposed

to bare metal, drug eluting stents are covered with a medicine that is slowly dispersed with the goal of suppressing the restenosis reaction. The key to the success of drug coating has been (a) choosing effective agents, (b) developing ways of adequately binding the drugs to the stainless surface of the stent struts (the coating must stay bound despite marked handling and stent deformation stresses) and (c) developing coating controlled release mechanisms that release the drug slowly over about 30 days.

See also

- Angiography
- Interventional cardiology
- Fractional flow reserve

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PET Scanning

Positron emission tomography (PET) is a nuclear medicine imaging technique which produces a three-dimensional image or picture of functional processes in the body. The system detects pairs of gamma rays emitted indirectly by a positron-emitting radionuclide (tracer), which is introduced into the body on a biologically active molecule. Images of tracer concentration in 3-dimensional or 4-dimensional space (the 4th dimension being time) within the body are then reconstructed by computer analysis. In modern scanners, this reconstruction is often accomplished with the aid of a CT X-ray scan performed on the patient during the same session, in the same machine.

If the biologically active molecule chosen for PET is FDG, an analogue of glucose, the concentrations of tracer imaged then give tissue metabolic activity, in terms of regional glucose uptake. Although use of this tracer results in the most common type of PET scan, other tracer molecules are used in PET to image the tissue concentration of many other types of molecules of interest.

History

The concept of emission and transmission tomography was introduced by David E. Kuhl and Roy Edwards in the late 1950s. Their work later led to the design and construction of several tomographic instruments at the University of Pennsylvania. Tomographic imaging techniques were further developed by Michel Ter-Pogossian, Michael E. Phelps and others at the Washington University School of Medicine.^{[1] [2]}

Work by Gordon Brownell, Charles Burnham and their associates at the Massachusetts General Hospital beginning in the 1950s contributed significantly to the development of PET technology and included the first demonstration of annihilation radiation for medical imaging.^[3] Their innovations, including the use of light pipes, and volumetric analysis have been important in the deployment of PET imaging. In 1961, James Robertson and his associates at Brookhaven National Laboratory built the first single-plane PET scan, nicknamed the "head-shrinker."^[4]

It is interesting that one of the factors most responsible for the acceptance of positron imaging was the development of radiopharmaceuticals. In particular, the development of labeled 2-fluorodeoxy-D-glucose (2FDG) by the Brookhaven group under the direction of Al Wolf and Joanna Fowler was a major factor in expanding the scope of PET imaging.^[5] The compound was first administered to two normal human volunteers by Abass Alavi in August 1976 at the University of Pennsylvania. Brain images obtained with an ordinary (non-PET) nuclear scanner demonstrated the concentration of FDG in that organ. Later, the substance was used in dedicated positron tomographic scanners, to yield the modern procedure.



Image of a typical positron emission tomography (PET) facility



PET/CT-System with 16-slice CT; the ceiling mounted device is an injection pump for CT contrast agent

The logical extension of positron instrumentation was a design using two 2-dimensional arrays. PC-I was the first instrument using this concept and was designed in 1968, completed in 1969 and reported in 1972. The first applications of PC-I in tomographic mode as distinguished from the computed tomographic mode were reported in 1970.^[6] It soon became clear to many of those involved in PET development that a circular or cylindrical array of detectors was the logical next step in PET instrumentation. Although many investigators took this approach, James Robertson^[7] and Z.H. Cho^[8] were the first to propose a ring system which has become the prototype of the current shape of PET.

The PET/CT scanner, attributed to Dr David Townsend and Dr Nutt was named by TIME Magazine as the medical invention of the year in 2000.

Description

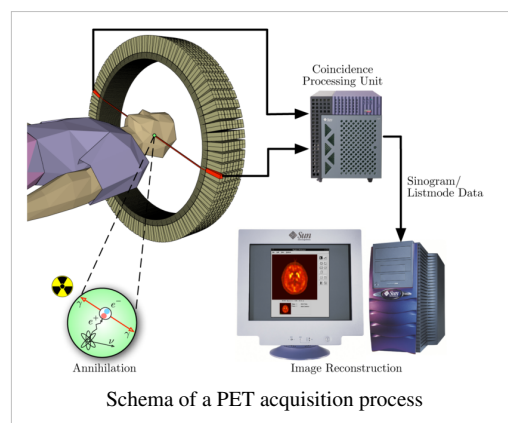
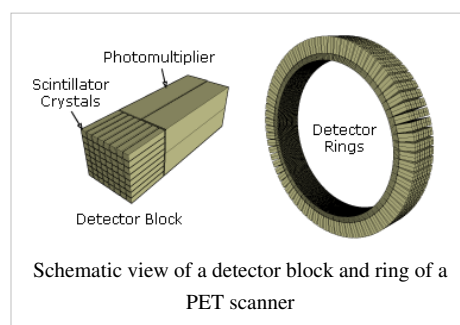
Operation

To conduct the scan, a short-lived radioactive tracer isotope is injected into the living subject (usually into blood circulation). The tracer is chemically incorporated into a biologically active molecule. There is a waiting period while the active molecule becomes concentrated in tissues of interest; then the subject is placed in the imaging scanner. The molecule most commonly used for this purpose is fluorodeoxyglucose (FDG), a sugar, for which the waiting period is typically an hour. During the scan a record of tissue concentration is made as the tracer decays.

As the radioisotope undergoes positron emission decay (also known as positive beta decay), it emits a positron, an antiparticle of the electron with opposite charge. The emitted positron travels in tissue for a short distance (typically less than 1 mm, but dependent on the isotope^[9]), during which time it loses kinetic energy, until it decelerates to a point where it can interact with an electron.^[10] The encounter annihilates both electron and positron, producing a pair of annihilation (gamma) photons moving in approximately opposite directions. These are detected when they reach a scintillator in the scanning device, creating a burst of light which is detected by photomultiplier tubes or silicon avalanche photodiodes (Si APD). The technique depends on simultaneous or coincident detection of the pair of photons moving in approximately opposite direction (it would be exactly opposite in their center of mass frame, but the scanner has no way to know this, and so has a built-in slight direction-error tolerance). Photons that do not arrive in temporal "pairs" (i.e. within a timing-window of a few nanoseconds) are ignored.

Localization of the positron annihilation event

The most significant fraction of electron-positron decays result in two 511 keV gamma photons being emitted at almost 180 degrees to each other; hence it is possible to localize their source along a straight line of coincidence (also called formally the **line of response** or **LOR**). In practice the LOR has a finite width as the emitted photons are not exactly 180 degrees apart. If the resolving time of the detectors is less than 500 picoseconds rather than about 10 nanoseconds, it is possible to localize the event to a segment of a chord, whose length is determined by the detector timing resolution. As the timing resolution improves, the signal-to-noise ratio (SNR) of the image will improve, requiring fewer events to achieve the same image quality. This technology is not yet common, but it is available on

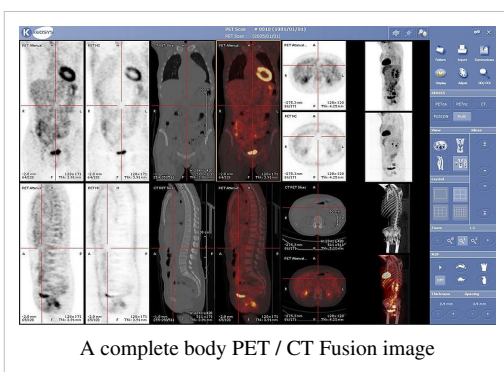


some new systems.^[11]

Image reconstruction using coincidence statistics

More commonly, a technique much like the reconstruction of computed tomography (CT) and single photon emission computed tomography (SPECT) data is used, although the data set collected in PET is much poorer than CT, so reconstruction techniques are more difficult (see Image reconstruction of PET).

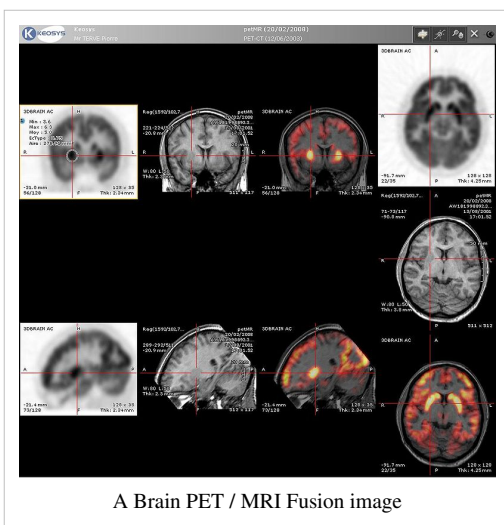
Using statistics collected from tens-of-thousands of coincidence events, a set of simultaneous equations for the total activity of each parcel of tissue along many LORs can be solved by a number of techniques, and thus a map of radioactivities as a function of location for parcels or bits of tissue (also called voxels), may be constructed and plotted. The resulting map shows the tissues in which the molecular tracer has become concentrated, and can be interpreted by a nuclear medicine physician or radiologist in the context of the patient's diagnosis and treatment plan.



Combination of PET with CT or MRI

PET scans are increasingly read alongside CT or magnetic resonance imaging (MRI) scans, the combination ("co-registration") giving both anatomic and metabolic information (i.e., what the structure is, and what it is doing biochemically). Because PET imaging is most useful in combination with anatomical imaging, such as CT, modern PET scanners are now available with integrated high-end multi-detector-row CT scanners. Because the two scans can be performed in immediate sequence during the same session, with the patient not changing position between the two types of scans, the two sets of images are more-precisely registered, so that areas of abnormality on the PET imaging can be more perfectly correlated with anatomy on the CT images. This is very useful in showing detailed views of moving organs or structures with higher anatomical variation, which is more common outside the brain.

At the Jülich Institute of Neurosciences and Biophysics, the world's largest PET/MRI device began operation in April 2009: a 9.4-tesla magnetic resonance tomograph (MRT) combined with a positron emission tomograph (PET). Presently, only the head and brain can be imaged at these high magnetic field strengths.^[12]



Radionuclides

Radionuclides used in PET scanning are typically isotopes with short half lives such as carbon-11 (~20 min), nitrogen-13 (~10 min), oxygen-15 (~2 min), and fluorine-18 (~110 min). These radionuclides are incorporated either into compounds normally used by the body such as glucose (or glucose analogues), water or ammonia, or into molecules that bind to receptors or other sites of drug action. Such labelled compounds are known as radiotracers. It is important to recognize that PET technology can be used to trace the biologic pathway of any compound in living humans (and many other species as well), provided it can be radiolabeled with a PET isotope. Thus the specific processes that can be probed with PET are virtually limitless, and radiotracers for new target molecules and processes are being synthesized all the time; as of this writing there are already dozens in clinical use and hundreds

applied in research. Presently, however, by far the most commonly used nuclide in clinical PET scanning is fluorine-18 in the form of FDG.

Due to the short half lives of most radioisotopes, the radiotracers must be produced using a cyclotron in close proximity to the PET imaging facility. The half life of fluorine-18 is long enough that it can be manufactured commercially at an offsite location.

Limitations

The minimization of radiation dose to the subject is an attractive feature of the use of short-lived radionuclides. Besides its established role as a diagnostic technique, PET has an expanding role as a method to assess the response to therapy, in particular, cancer therapy,^[13] where the risk to the patient from lack of knowledge about disease progress is much greater than the risk from the test radiation.

Limitations to the widespread use of PET arise from the high costs of cyclotrons needed to produce the short-lived radionuclides for PET scanning and the need for specially adapted on-site chemical synthesis apparatus to produce the radiopharmaceuticals. Few hospitals and universities are capable of maintaining such systems, and most clinical PET is supported by third-party suppliers of radiotracers which can supply many sites simultaneously. This limitation restricts clinical PET primarily to the use of tracers labelled with fluorine-18, which has a half life of 110 minutes and can be transported a reasonable distance before use, or to rubidium-82, which can be created in a portable generator and is used for myocardial perfusion studies. Nevertheless, in recent years a few on-site cyclotrons with integrated shielding and hot labs have begun to accompany PET units to remote hospitals. The presence of the small on-site cyclotron promises to expand in the future as the cyclotrons shrink in response to the high cost of isotope transportation to remote PET machines^[14]

Because the half-life of fluorine-18 is about two hours, the prepared dose of a radiopharmaceutical bearing this radionuclide will undergo multiple half-lives of decay during the working day. This necessitates frequent recalibration of the remaining dose (determination of activity per unit volume) and careful planning with respect to patient scheduling.

Image reconstruction

The raw data collected by a PET scanner are a list of 'coincidence events' representing near-simultaneous detection of annihilation photons by a pair of detectors. Each coincidence event represents a line in space connecting the two detectors along which the positron emission occurred. Modern systems with a high time resolution also use a technique (called "Time-of-flight") where they more precisely decide the difference in time between the detection of the two photons and can thus limit the length of the earlier mentioned line to around 10 cm.

Coincidence events can be grouped into projections images, called sinograms. The sinograms are sorted by the angle of each view and tilt, the latter in 3D case images. The sinogram images are analogous to the projections captured by computed tomography (CT) scanners, and can be reconstructed in a similar way. However, the statistics of the data is much worse than those obtained through transmission tomography. A normal PET data set has millions of counts for the whole acquisition, while the CT can reach a few billion counts. As such, PET data suffer from scatter and random events much more dramatically than CT data does.

In practice, considerable pre-processing of the data is required - correction for random coincidences, estimation and subtraction of scattered photons, detector dead-time correction (after the detection of a photon, the detector must "cool down" again) and detector-sensitivity correction (for both inherent detector sensitivity and changes in sensitivity due to angle of incidence).

Filtered back projection (FBP) has been frequently used to reconstruct images from the projections. This algorithm has the advantage of being simple while having a low requirement for computing resources. However, shot noise in the raw data is prominent in the reconstructed images and areas of high tracer uptake tend to form streaks across the image.

Iterative expectation-maximization algorithms are now the preferred method of reconstruction. The advantage is a better noise profile and resistance to the streak artifacts common with FBP, but the disadvantage is higher computer resource requirements.

Attenuation correction: As different LORs must traverse different thicknesses of tissue, the photons are attenuated differentially. The result is that structures deep in the body are reconstructed as having falsely low tracer uptake. Contemporary scanners can estimate attenuation using integrated x-ray CT equipment, however earlier equipment offered a crude form of CT using a gamma ray (positron emitting) source and the PET detectors.

While attenuation-corrected images are generally more faithful representations, the correction process is itself susceptible to significant artifacts. As a result, both corrected and uncorrected images are always reconstructed and read together.

2D/3D reconstruction: Early PET scanners had only a single ring of detectors, hence the acquisition of data and subsequent reconstruction was restricted to a single transverse plane. More modern scanners now include multiple rings, essentially forming a cylinder of detectors.

There are two approaches to reconstructing data from such a scanner: 1) treat each ring as a separate entity, so that only coincidences within a ring are detected, the image from each ring can then be reconstructed individually (2D reconstruction), or 2) allow coincidences to be detected between rings as well as within rings, then reconstruct the entire volume together (3D).

3D techniques have better sensitivity (because more coincidences are detected and used) and therefore less noise, but are more sensitive to the effects of scatter and random coincidences, as well as requiring correspondingly greater computer resources. The advent of sub-nanosecond timing resolution detectors affords better random coincidence rejection, thus favoring 3D image reconstruction.

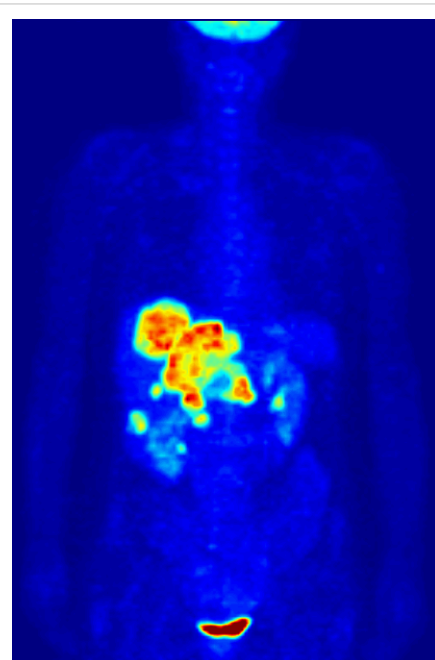
Applications

PET is both a medical and research tool. It is used heavily in clinical oncology (medical imaging of tumors and the search for metastases), and for clinical diagnosis of certain diffuse brain diseases such as those causing various types of dementias. PET is also an important research tool to map normal human brain and heart function.

PET is also used in pre-clinical studies using animals, where it allows repeated investigations into the same subjects. This is particularly valuable in cancer research, as it results in an increase in the statistical quality of the data (subjects can act as their own control) and substantially reduces the numbers of animals required for a given study.

Alternative methods of scanning include x-ray computed tomography (CT), magnetic resonance imaging (MRI) and functional magnetic resonance imaging (fMRI), ultrasound and single photon emission computed tomography (SPECT).

While some imaging scans such as CT and MRI isolate organic anatomic changes in the body, PET and SPECT are capable of detecting areas of molecular biology detail (even prior to anatomic change). PET scanning does this using radiolabelled molecular probes that have different rates of uptake depending on the type and function of tissue involved. Changing of regional blood flow in various anatomic structures (as a measure of the injected positron emitter) can be visualized and relatively quantified with a PET scan.



Maximum intensity projection (MIP) of a F-18 FDG wholebody PET acquisition; liver metastases of a colorectal tumor are clearly visible within the abdominal region of the image. Normal physiological isotope uptake is seen in the brain, renal collection systems and bladder. In this animation, it is important to view the subject as rotating clockwise (note liver position).

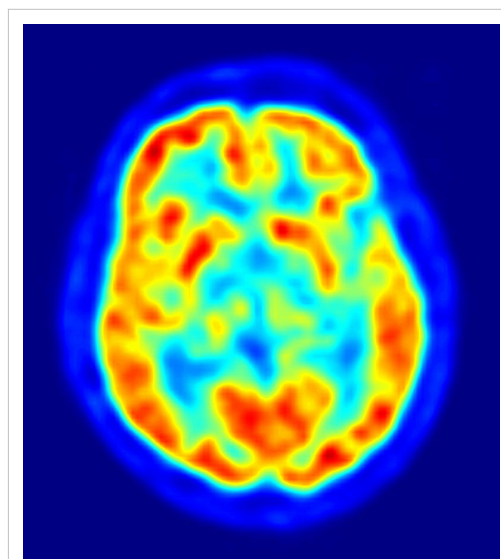
PET imaging is best performed using a dedicated PET scanner. However, it is possible to acquire PET images using a conventional dual-head gamma camera fitted with a coincidence detector. The quality of gamma-camera PET is considerably lower, and acquisition is slower. However, for institutions with low demand for PET, this may allow on-site imaging, instead of referring patients to another center, or relying on a visit by a mobile scanner.

PET is a valuable technique for some diseases and disorders, because it is possible to target the radio-chemicals used for particular bodily functions.

1. **Oncology:** PET scanning with the tracer fluorine-18 (F-18) fluorodeoxyglucose (FDG), called FDG-PET, is widely used in clinical oncology. This tracer is a glucose analog that is taken up by glucose-using cells and phosphorylated by hexokinase (whose mitochondrial form is greatly elevated in rapidly growing malignant tumours). A typical dose of FDG used in an oncological scan is 200-400 MBq for an adult human. Because the oxygen atom which is replaced by F-18 to generate FDG is required for the next step in glucose metabolism in all cells, no further reactions occur in FDG. Furthermore, most tissues (with the notable exception of liver and kidneys) cannot remove the phosphate added by hexokinase. This means that FDG is trapped in any cell which takes it up, until it decays, since phosphorylated sugars, due to their ionic charge, cannot exit from the cell. This results in intense radiolabeling of tissues with high glucose uptake, such as the brain, the liver, and most cancers. As a result, FDG-PET can be used for diagnosis, staging, and monitoring treatment of cancers, particularly in Hodgkin's lymphoma, non-Hodgkin lymphoma, and lung cancer. Many other types of solid tumors will be found to be very highly labeled on a case-by-case basis—a fact which becomes especially useful in searching for tumor metastasis, or for recurrence after a known highly active primary tumor is removed. Because individual PET scans are more expensive than "conventional" imaging with computed tomography (CT) and magnetic resonance imaging (MRI), expansion of FDG-PET in cost-constrained health services will depend on proper health

technology assessment; this problem is a difficult one because structural and functional imaging often cannot be directly compared, as they provide different information. Oncology scans using FDG make up over 90% of all PET scans in current practice.

Neurology: PET neuroimaging is based on an assumption that areas of high radioactivity are associated with brain activity. What is actually measured indirectly is the flow of blood to different parts of the brain, which is generally believed to be correlated, and has been measured using the tracer oxygen-15. However, because of its 2-minute half-life O-15 must be piped directly from a medical cyclotron for such uses, and this is difficult. In practice, since the brain is normally a rapid user of glucose, and since brain pathologies such as Alzheimer's disease greatly decrease brain metabolism of both glucose and oxygen in tandem, standard FDG-PET of the brain, which measures regional glucose use, may also be successfully used to differentiate Alzheimer's disease from other dementing processes, and also to make early diagnosis of Alzheimer's disease. The advantage of FDG-PET for these uses is its much wider availability. PET imaging with FDG can also be used for localization of seizure focus: A seizure focus will appear



PET scan of the human brain.

as hypometabolic during an interictal scan. Several radiotracers (i.e. radioligands) have been developed for PET that are ligands for specific neuroreceptor subtypes such as [^{11}C] raclopride and [^{18}F] fallypride for dopamine D2/D3 receptors, [^{11}C]McN 5652 and [^{11}C]DASB for serotonin transporters, or enzyme substrates (e.g. 6-FDOPA for the AADC enzyme). These agents permit the visualization of neuroreceptor pools in the context of a plurality of neuropsychiatric and neurologic illnesses. A novel probe developed at the University of Pittsburgh termed PIB (Pittsburgh compound B) permits the visualization of amyloid plaques in the brains of Alzheimer's patients. This technology could assist clinicians in making a positive clinical diagnosis of AD pre-mortem and aid in the development of novel anti-amyloid therapies. [^{11}C]PMP (N-[^{11}C]methylpiperidin-4-yl propionate) is a novel radiopharmaceutical used in PET imaging to determine the activity of the acetylcholinergic neurotransmitter system by acting as a substrate for acetylcholinesterase. Post-mortem examination of AD patients have shown decreased levels of acetylcholinesterase. [^{11}C]PMP is used to map the acetylcholinesterase activity in the brain which could allow for pre-mortem diagnosis of AD and help to monitor AD treatments.^[15] Avid Radiopharmaceuticals of Philadelphia has developed a compound called 18F-AV-45 that uses the longer-lasting radionuclide fluorine-18 to detect amyloid plaques using PET scans.^[16]

3. **Cardiology, atherosclerosis and vascular disease study:** In clinical cardiology, FDG-PET can identify so-called "hibernating myocardium", but its cost-effectiveness in this role versus SPECT is unclear. Recently, a role has been suggested for FDG-PET imaging of atherosclerosis to detect patients at risk of stroke [17].
4. **Neuropsychology / Cognitive neuroscience:** To examine links between specific psychological processes or disorders and brain activity.
5. **Psychiatry:** Numerous compounds that bind selectively to neuroreceptors of interest in biological psychiatry have been radiolabeled with C-11 or F-18. Radioligands that bind to dopamine receptors (D1,D2, reuptake transporter), serotonin receptors (5HT1A, 5HT2A, reuptake transporter) opioid receptors (μ) and other sites have been used successfully in studies with human subjects. Studies have been performed examining the state of these receptors in patients compared to healthy controls in schizophrenia, substance abuse, mood disorders and other psychiatric conditions.
6. **Pharmacology:** In pre-clinical trials, it is possible to radiolabel a new drug and inject it into animals. Such scans are referred to as biodistribution studies. The uptake of the drug, the tissues in which it concentrates, and its

eventual elimination, can be monitored far more quickly and cost effectively than the older technique of killing and dissecting the animals to discover the same information. Much more commonly, however, drug occupancy at a purported site of action can be inferred indirectly by competition studies between unlabeled drug and radiolabeled compounds known apriori to bind with specificity to the site. A single radioligand can be used this way to test many potential drug candidates for the same target. A related technique involves scanning with radioligands that compete with an endogenous (naturally occurring) substance at a given receptor to demonstrate that a drug causes the release of the natural substance.

7. PET technology for small animal imaging: A miniature PET tomograph has been constructed that is small enough for a fully conscious and mobile rat to wear on its head while walking around.^[18] This RatCAP (Rat Conscious Animal PET) allows animals to be scanned without the confounding effects of anesthesia. PET scanners designed specifically for imaging rodents or small primates are marketed for academic and pharmaceutical research.
8. Musculo-Skeletal Imaging: PET has been shown to be a feasible technique for studying skeletal muscles during exercises like walking.^[19] One of the main advantages of using PET is that it can also provide muscle activation data about deeper lying muscles such as the vastus intermedius and the gluteus minimus, as compared to other muscle studying techniques like Electromyography, which can only be used on superficial muscles (i.e. directly under the skin). A clear disadvantage, however, is that PET provides no timing information about muscle activation, because it has to be measured after the exercise is completed. This is due to the time it takes for FDG to accumulate in the activated muscles.

Pulse Shape Discrimination

The pulse Shape Discrimination (PSD) is a technique used to define which pulse is related to each crystal. Different Techniques were introduced to discriminate between two-types of pulses according to its shape (indeed due to the decay time).

Safety

PET scanning is non-invasive, but it does involve exposure to ionizing radiation. The total dose of radiation is not insignificant, usually around 5–7 mSv. However, in modern practice, a combined PET/CT scan is almost always performed, and for PET/CT scanning, the radiation exposure may be substantial - around 23–26 mSv (for a 70 kg person - dose is likely to be higher for higher body weights).^[20] When compared to the classification level for radiation workers in the UK, of 6 mSv it can be seen that PET scans need proper justification. This can also be compared to 2.2 mSv average annual background radiation in the UK, 0.02 mSv for a chest x-ray and 6.5 - 8 mSv for a CT scan of the chest, according to the Chest Journal and ICRP.^{[21] [22]} A policy change suggested by the IFALPA member associations in year 1999 mentioned that an aircrew member is likely to receive a radiation dose of 4–9 mSv per year.^[23]

See also

- Diffuse optical imaging
- Hot cell (Equipment used to produce the radiopharmaceuticals used in PET)
- Molecular Imaging

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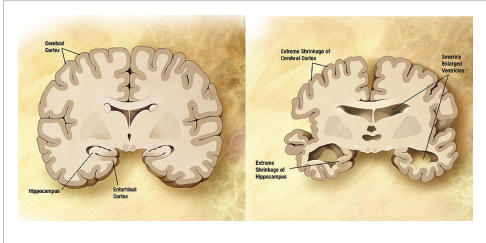
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External links

- PET Images (http://rad.usuhs.edu/medpix/master.php3?mode=image_finder&action=search&srchstr=&srch_type=all&labels=&details=2&no_filter=2&plane_id=&capt_id=-4&filter_m=modality&filter_o=&acr_pre=&filter_p=&acr_post=#top) Search MedPix(r)
- Seeing is believing: In vivo functional real-time imaging of transplanted islets using positron emission tomography (PET)(a protocol) (http://www.natureprotocols.com/2006/12/21/seeing_is_believing_in_vivo_fu_1.php), Nature Protocols, from Nature Medicine - 12, 1423 - 1428 (2006).
- The nuclear medicine and molecular medicine podcast (<http://nucast.com>) - Podcast
- Positron Emission Particle Tracking (<http://www.np.ph.bham.ac.uk/pic/pept.htm>) (PEPT) - engineering analysis tool based on PET that is able to track single particles in 3D within mixing systems or fluidised beds. Developed at the University of Birmingham, UK.
- CMS coverage of PET scans (http://www.hematologytimes.com/ht/p_article.do?id=948)
- PET-CT atlas Harvard Medical School (<http://www.med.harvard.edu/JPNM/chetan/>)

Alzheimer's disease

Alzheimer's disease	
Classification and external resources	
 Comparison of a normal aged brain (left) and an Alzheimer's patient's brain (right). Differential characteristics are pointed out.	
ICD-10	G 30. ^[1] , F 00. ^[2]
ICD-9	331.0 ^[3] , 290.1 ^[4]
OMIM	104300 ^[5]
DiseasesDB	490 ^[6]
MedlinePlus	000760 ^[7]
eMedicine	neuro/13 ^[8]
MeSH	D000544 ^[9]
GeneReviews	^[10]

Alzheimer's disease (AD)—also called **Alzheimer disease**, **senile dementia of the Alzheimer type (SDAT)**, **primary degenerative dementia of the Alzheimer's type (PDDAT)**, or **Alzheimer's**—is the most common form of dementia. This incurable, degenerative, and terminal disease was first described by German psychiatrist and neuropathologist Alois Alzheimer in 1906 and was named after him.^[11] Most often, it is diagnosed in people over 65 years of age,^[12] although the less-prevalent early-onset Alzheimer's can occur much earlier. In 2006, there were 26.6 million sufferers worldwide. Alzheimer's is predicted to affect 1 in 85 people globally by 2050.^[13]

Although the course of Alzheimer's disease is unique for every individual, there are many common symptoms.^[14] The earliest observable symptoms are often mistakenly thought to be 'age-related' concerns, or manifestations of stress.^[15] In the early stages, the most commonly recognised symptom is inability to acquire new memories, such as difficulty in recalling recently observed facts. When AD is suspected, the diagnosis is usually confirmed with behavioural assessments and cognitive tests, often followed by a brain scan if available.^[16]

As the disease advances, symptoms include confusion, irritability and aggression, mood swings, language breakdown, long-term memory loss, and the general withdrawal of the sufferer as their senses decline.^[15] ^[17] Gradually, bodily functions are lost, ultimately leading to death.^[18] Individual prognosis is difficult to assess, as the duration of the disease varies. AD develops for an indeterminate period of time before becoming fully apparent, and it can progress undiagnosed for years. The mean life expectancy following diagnosis is approximately seven years.^[19] Fewer than three percent of individuals live more than fourteen years after diagnosis.^[20]

The cause and progression of Alzheimer's disease are not well understood. Research indicates that the disease is associated with plaques and tangles in the brain.^[21] Currently used treatments offer a small symptomatic benefit; no treatments to delay or halt the progression of the disease are as yet available. As of 2008, more than 500 clinical trials have been conducted for identification of a possible treatment for AD, but it is unknown if any of the tested

intervention strategies will show promising results.^[22] A number of non-invasive, life-style habits have been suggested for the prevention of Alzheimer's disease, but there is a lack of adequate evidence for a link between these recommendations and reduced degeneration. Mental stimulation, exercise, and a balanced diet are suggested, as both a possible prevention and a sensible way of managing the disease.^[23]

Because AD cannot be cured and is degenerative, management of patients is essential. The role of the main caregiver is often taken by the spouse or a close relative.^[24] Alzheimer's disease is known for placing a great burden on caregivers; the pressures can be wide-ranging, involving social, psychological, physical, and economic elements of the caregiver's life.^{[25] [26] [27]} In developed countries, AD is one of the most costly diseases to society.^{[28] [29]}

Characteristics

The disease course is divided into four stages, with progressive patterns of cognitive and functional impairments.

Pre-dementia

The first symptoms are often mistaken as related to aging or stress.^[15] Detailed neuropsychological testing can reveal mild cognitive difficulties up to eight years before a person fulfills the clinical criteria for diagnosis of AD.^[30] These early symptoms can affect the most complex daily living activities.^[31] The most noticeable deficit is memory loss, which shows up as difficulty in remembering recently learned facts and inability to acquire new information.^[30]^[32]

Subtle problems with the executive functions of attentiveness, planning, flexibility, and abstract thinking, or impairments in semantic memory (memory of meanings, and concept relationships), can also be symptomatic of the early stages of AD.^[30] Apathy can be observed at this stage, and remains the most persistent neuropsychiatric symptom throughout the course of the disease.^[33] The preclinical stage of the disease has also been termed mild cognitive impairment,^[32] but whether this term corresponds to a different diagnostic stage or identifies the first step of AD is a matter of dispute.^[34]

Early

In people with AD the increasing impairment of learning and memory eventually leads to a definitive diagnosis. In a small portion of them, difficulties with language, executive functions, perception (agnosia), or execution of movements (apraxia) are more prominent than memory problems.^[35] AD does not affect all memory capacities equally. Older memories of the person's life (episodic memory), facts learned (semantic memory), and implicit memory (the memory of the body on how to do things, such as using a fork to eat) are affected to a lesser degree than new facts or memories.^{[36] [37]}

Language problems are mainly characterised by a shrinking vocabulary and decreased word fluency, which lead to a general impoverishment of oral and written language.^{[35] [38]} In this stage, the person with Alzheimer's is usually capable of adequately communicating basic ideas.^{[35] [38] [39]} While performing fine motor tasks such as writing, drawing or dressing, certain movement coordination and planning difficulties (apraxia) may be present but they are commonly unnoticed.^[35] As the disease progresses, people with AD can often continue to perform many tasks independently, but may need assistance or supervision with the most cognitively demanding activities.^[35]

Moderate

Progressive deterioration eventually hinders independence; with subjects being unable to perform most common activities of daily living.^[35] Speech difficulties become evident due to an inability to recall vocabulary, which leads to frequent incorrect word substitutions (paraphasias). Reading and writing skills are also progressively lost.^{[35] [39]} Complex motor sequences become less coordinated as time passes and AD progresses, so the risk of falling increases.^[35] During this phase, memory problems worsen, and the person may fail to recognise close relatives.^[35]

Long-term memory, which was previously intact, becomes impaired.^[35]

Behavioural and neuropsychiatric changes become more prevalent. Common manifestations are wandering, irritability and labile affect, leading to crying, outbursts of unpremeditated aggression, or resistance to caregiving.^[35] Sundowning can also appear.^[40] Approximately 30% of patients develop illusionary misidentifications and other delusional symptoms.^[35] Subjects also lose insight of their disease process and limitations (anosognosia).^[35] Urinary incontinence can develop.^[35] These symptoms create stress for relatives and caretakers, which can be reduced by moving the person from home care to other long-term care facilities.^[35] [41]

Advanced

During this last stage of AD, the patient is completely dependent upon caregivers.^[35] Language is reduced to simple phrases or even single words, eventually leading to complete loss of speech.^[35] [39] Despite the loss of verbal language abilities, patients can often understand and return emotional signals.^[35] Although aggressiveness can still be present, extreme apathy and exhaustion are much more common results.^[35] Patients will ultimately not be able to perform even the most simple tasks without assistance.^[35] Muscle mass and mobility deteriorate to the point where they are bedridden, and they lose the ability to feed themselves.^[35] AD is a terminal illness with the cause of death typically being an external factor such as infection of pressure ulcers or pneumonia, not the disease itself.^[35]

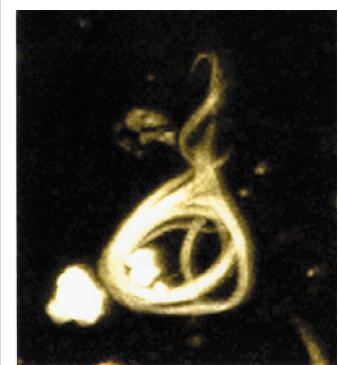
Causes

Several competing hypotheses exist trying to explain the cause of the disease. The oldest, on which most currently available drug therapies are based, is the *cholinergic hypothesis*,^[42] which proposes that AD is caused by reduced synthesis of the neurotransmitter acetylcholine. The cholinergic hypothesis has not maintained widespread support, largely because medications intended to treat acetylcholine deficiency have not been very effective. Other cholinergic effects have also been proposed, for example, initiation of large-scale aggregation of amyloid,^[43] leading to generalised neuroinflammation.^[44]

In 1991, the *amyloid hypothesis* postulated that amyloid beta ($A\beta$) deposits are the fundamental cause of the disease.^[45] [46] Support for this postulate comes from the location of the gene for the amyloid beta precursor protein (APP) on chromosome 21, together with the fact that people with trisomy 21 (Down Syndrome) who have an extra gene copy almost universally exhibit AD by 40 years of age.^[47] [48] Also APOE4, the major genetic risk factor for AD, leads to excess amyloid buildup in the brain before AD symptoms arise. Thus, $A\beta$ deposition precedes clinical AD.^[49] Further evidence comes from the finding that transgenic mice that express a mutant form of the human APP gene develop fibrillar amyloid plaques and Alzheimer's-like brain pathology with spatial learning deficits.^[50]

An experimental vaccine was found to clear the amyloid plaques in early human trials, but it did not have any significant effect on dementia.^[51] Researchers have been led to suspect non-plaque $A\beta$ oligomers (aggregates of many monomers) as the primary pathogenic form of $A\beta$. These toxic oligomers, also referred to as amyloid-derived diffusible ligands (ADDLs), bind to a surface receptor on neurons and change the structure of the synapse, thereby disrupting neuronal communication.^[52] One receptor for $A\beta$ oligomers may be the prion protein, the same protein that has been linked to mad cow disease and the related human condition, Creutzfeldt-Jakob disease, thus potentially linking the underlying mechanism of these neurodegenerative disorders with that of Alzheimer's disease.^[53]

In 2009, this theory was updated, suggesting that a close relative of the beta-amyloid protein, and not necessarily the beta-amyloid itself, may be a major culprit in the disease. The theory holds that an amyloid-related mechanism that prunes neuronal connections in the brain in the fast-growth phase of early life may be triggered by aging-related



Microscopy image of a neurofibrillary tangle, conformed by hyperphosphorylated tau protein

processes in later life to cause the neuronal withering of Alzheimer's disease.^[54] N-APP, a fragment of APP from the peptide's N-terminus, is adjacent to beta-amyloid and is cleaved from APP by one of the same enzymes. N-APP triggers the self-destruct pathway by binding to a neuronal receptor called death receptor 6 (DR6, also known as TNFRSF21).^[54] DR6 is highly expressed in the human brain regions most affected by Alzheimer's, so it is possible that the N-APP/DR6 pathway might be hijacked in the aging brain to cause damage. In this model, beta-amyloid plays a complementary role, by depressing synaptic function.

A 2004 study found that deposition of amyloid plaques does not correlate well with neuron loss.^[55] This observation supports the *tau hypothesis*, the idea that tau protein abnormalities initiate the disease cascade.^[46] In this model, hyperphosphorylated tau begins to pair with other threads of tau. Eventually, they form neurofibrillary tangles inside nerve cell bodies.^[56] When this occurs, the microtubules disintegrate, collapsing the neuron's transport system.^[57] This may result first in malfunctions in biochemical communication between neurons and later in the death of the cells.^[58] Herpes simplex virus type 1 has also been proposed to play a causative role in people carrying the susceptible versions of the apoE gene.^[59]

Another hypothesis asserts that the disease may be caused by age-related myelin breakdown in the brain. Demyelination leads to axonal transport disruptions, leading to loss of neurons that become stale. Iron released during myelin breakdown is hypothesized to cause further damage. Homeostatic myelin repair processes contribute to the development of proteinaceous deposits such as amyloid-beta and tau.^{[60] [61] [62]}

Oxidative stress is a significant cause in the formation of the pathology.^[63]

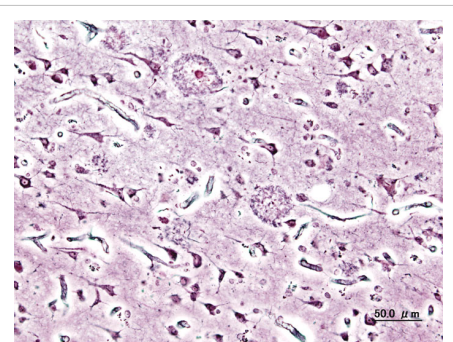
AD individuals show 70% loss of locus coeruleus cells that provide norepinephrine (in addition to its neurotransmitter role) that locally diffuses from "varicosities" as an endogenous antiinflammatory agent in the microenvironment around the neurons, glial cells, and blood vessels in the neocortex and hippocampus.^[64] It has been shown that norepinephrine stimulates mouse microglia to suppress A β -induced production of cytokines and their phagocytosis of A β .^[64] This suggests that degeneration of the locus ceruleus might be responsible for increased A β deposition in AD brains.^[64]

Pathophysiology

Neuropathology

Alzheimer's disease is characterised by loss of neurons and synapses in the cerebral cortex and certain subcortical regions. This loss results in gross atrophy of the affected regions, including degeneration in the temporal lobe and parietal lobe, and parts of the frontal cortex and cingulate gyrus.^[44] Studies using MRI and PET have documented reductions in the size of specific brain regions in patients as they progressed from mild cognitive impairment to Alzheimer's disease, and in comparison with similar images from healthy older adults.^[65]

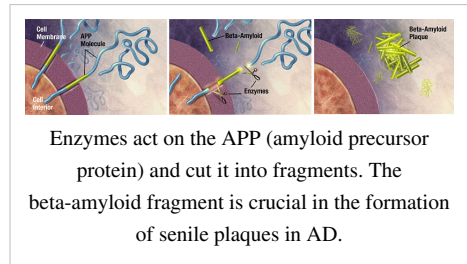
Both amyloid plaques and neurofibrillary tangles are clearly visible by microscopy in brains of those afflicted by AD.^[21] Plaques are dense, mostly insoluble deposits of amyloid-beta peptide and cellular material outside and around neurons. Tangles (neurofibrillary tangles) are aggregates of the microtubule-associated protein tau which has become hyperphosphorylated and accumulate inside the cells themselves. Although many older individuals develop some plaques and tangles as a consequence of aging, the brains of AD patients have a greater number of them in specific brain regions such as the temporal lobe.^[66] Lewy bodies are not rare in AD patient's brains.^[67]



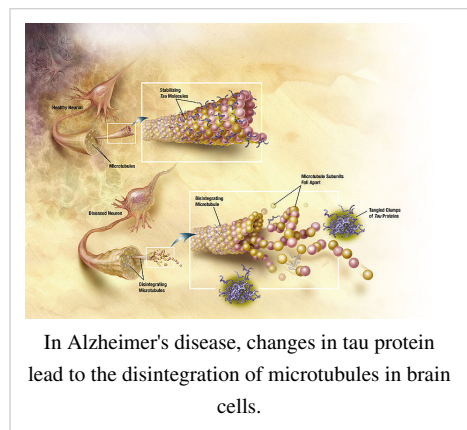
Histopathologic image of senile plaques seen in the cerebral cortex of a person with Alzheimer's disease of presenile onset. Silver impregnation.

Biochemistry

Alzheimer's disease has been identified as a protein misfolding disease (proteopathy), caused by accumulation of abnormally folded A-beta and tau proteins in the brain.^[68] Plaques are made up of small peptides, 39–43 amino acids in length, called beta-amyloid (also written as A-beta or A β). Beta-amyloid is a fragment from a larger protein called amyloid precursor protein (APP), a transmembrane protein that penetrates through the neuron's membrane. APP is critical to neuron growth, survival and post-injury repair.^{[69] [70]} In Alzheimer's disease, an unknown process causes APP to be divided into smaller fragments by enzymes through proteolysis.^[71] One of these fragments gives rise to fibrils of beta-amyloid, which form clumps that deposit outside neurons in dense formations known as senile plaques.^{[21] [72]}



AD is also considered a tauopathy due to abnormal aggregation of the tau protein. Every neuron has a cytoskeleton, an internal support structure partly made up of structures called microtubules. These microtubules act like tracks, guiding nutrients and molecules from the body of the cell to the ends of the axon and back. A protein called *tau* stabilizes the microtubules when phosphorylated, and is therefore called a microtubule-associated protein. In AD, tau undergoes chemical changes, becoming hyperphosphorylated; it then begins to pair with other threads, creating neurofibrillary tangles and disintegrating the neuron's transport system.^[73]



Disease mechanism

Exactly how disturbances of production and aggregation of the beta amyloid peptide gives rise to the pathology of AD is not known.^[74] The amyloid hypothesis traditionally points to the accumulation of beta amyloid peptides as the central event triggering neuron degeneration. Accumulation of aggregated amyloid fibrils, which are believed to be the toxic form of the protein responsible for disrupting the cell's calcium ion homeostasis, induces programmed cell death (apoptosis).^[75] It is also known that A β selectively builds up in the mitochondria in the cells of Alzheimer's-affected brains, and it also inhibits certain enzyme functions and the utilisation of glucose by neurons.^[76]

Various inflammatory processes and cytokines may also have a role in the pathology of Alzheimer's disease. Inflammation is a general marker of tissue damage in any disease, and may be either secondary to tissue damage in AD or a marker of an immunological response.^[77]

Alterations in the distribution of different neurotrophic factors and in the expression of their receptors such as the brain derived neurotrophic factor (BDNF) have been described in AD.^{[78] [79]}

Genetics

The vast majority of cases of Alzheimer's disease are sporadic, meaning that they are not genetically inherited although some genes may act as risk factors. On the other hand, around 0.1% of the cases are familial forms of autosomal-dominant inheritance, which usually have an onset before age 65.^[80]

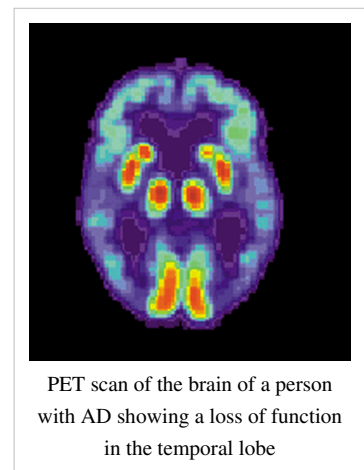
Most of autosomal dominant familial AD can be attributed to mutations in one of three genes: amyloid precursor protein (APP) and presenilins 1 and 2.^[81] Most mutations in the APP and presenilin genes increase the production of a small protein called A β 42, which is the main component of senile plaques.^[82] Some of the mutations merely alter the size ratio between A β 42 and the other major forms—e.g., A β 40—without increasing A β 42 levels.^[82]^[83] This suggests that presenilin mutations can cause disease even if they lower the total amount of A β produced and may point to other roles of presenilin or a role for alterations in the function of APP and/or its fragments other than A β .

Most cases of Alzheimer's disease do not exhibit autosomal-dominant inheritance and are termed sporadic AD. Nevertheless genetic differences may act as risk factors. The best known genetic risk factor is the inheritance of the ϵ 4 allele of the apolipoprotein E (APOE).^[84]^[85] Between 40 and 80% of patients with AD possess at least one apoE4 allele.^[85] The APOE4 allele increases the risk of the disease by three times in heterozygotes and by 15 times in homozygotes.^[80] Geneticists agree that numerous other genes also act as risk factors or have protective effects that influence the development of late onset Alzheimer's disease.^[81] Over 400 genes have been tested for association with late-onset sporadic AD,^[81] most with null results.^[80]

Diagnosis

Alzheimer's disease is usually diagnosed clinically from the patient history, collateral history from relatives, and clinical observations, based on the presence of characteristic neurological and neuropsychological features and the absence of alternative conditions.^[86]^[87] Advanced medical imaging with computed tomography (CT) or magnetic resonance imaging (MRI), and with single photon emission computed tomography (SPECT) or positron emission tomography (PET) can be used to help exclude other cerebral pathology or subtypes of dementia.^[88] Moreover, it may predict conversion from prodromal stages (mild cognitive impairment) to Alzheimer's disease.^[89]

Assessment of intellectual functioning including memory testing can further characterise the state of the disease.^[15] Medical organisations have created diagnostic criteria to ease and standardise the diagnostic process for practicing physicians. The diagnosis can be confirmed with very high accuracy post-mortem when brain material is available and can be examined histologically.^[90]



Diagnostic criteria

The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA, now known as the Alzheimer's Association) established the most commonly used NINCDS-ADRDA Alzheimer's Criteria for diagnosis in 1984,^[90] extensively updated in 2007.^[91] These criteria require that the presence of cognitive impairment, and a suspected dementia syndrome, be confirmed by neuropsychological testing for a clinical diagnosis of possible or probable AD. A histopathologic confirmation including a microscopic examination of brain tissue is required for a definitive diagnosis. Good statistical reliability and validity have been shown between the diagnostic criteria and definitive histopathological confirmation.^[92] Eight cognitive domains are most commonly impaired in AD—memory, language, perceptual skills, attention, constructive abilities, orientation, problem solving and functional abilities. These domains are equivalent to the NINCDS-ADRDA Alzheimer's Criteria as listed in the *Diagnostic and Statistical Manual of Mental*

Disorders (DSM-IV-TR) published by the American Psychiatric Association.^{[93] [94]}

Diagnostic tools

Neuropsychological tests such as the mini-mental state examination (MMSE), are widely used to evaluate the cognitive impairments needed for diagnosis. More comprehensive test arrays are necessary for high reliability of results, particularly in the earliest stages of the disease.^{[95] [96]} Neurological examination in early AD will usually provide normal results, except for obvious cognitive impairment, which may not differ from that resulting from other diseases processes, including other causes of dementia.

Further neurological examinations are crucial in the differential diagnosis of AD and other diseases.^[15] Interviews with family members are also utilised in the assessment of the disease. Caregivers can supply important information on the daily living abilities, as well as on the decrease, over time, of the person's mental function.^[89] A caregiver's viewpoint is particularly important, since a person with AD is commonly unaware of his own deficits.^[97] Many times, families also have difficulties in the detection of initial dementia symptoms and may not communicate accurate information to a physician.^[98]

Another recent objective marker of the disease is the analysis of cerebrospinal fluid for amyloid beta or tau proteins,^[99] both total tau protein and phosphorylated tau_{181P} protein concentrations.^[100] Searching for these proteins using a spinal tap can predict the onset of Alzheimer's with a sensitivity of between 94% and 100%.^[100] When used in conjunction with existing neuroimaging techniques, doctors can identify patients with significant memory loss who are already developing the disease.^[100] Spinal fluid tests are commercially available, unlike the latest neuroimaging technology.^[101] Alzheimer's was diagnosed in one-third of the people who did not have any symptoms in a 2010 study, meaning that disease progression occurs well before symptoms occur.^[102]

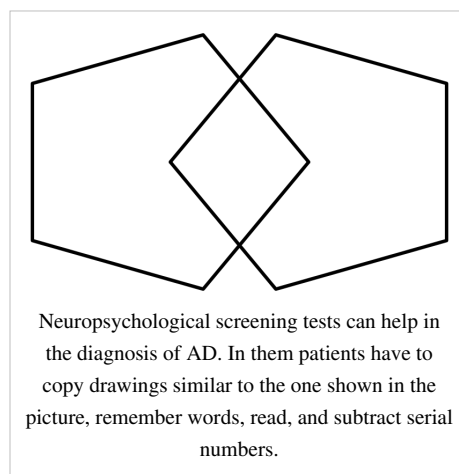
Supplemental testing provides extra information on some features of the disease or is used to rule out other diagnoses. Blood tests can identify other causes for dementia than AD^[15] —causes which may, in rare cases, be reversible.^[103] It is common to perform thyroid function tests, assess B12, rule out syphilis, rule out metabolic problems (including tests for kidney function, electrolyte levels and for diabetes), assess levels of heavy metals (e.g. lead, mercury) and anemia. (See differential diagnosis for Dementia). (It is also necessary to rule out delirium).

Psychological tests for depression are employed, since depression can either be concurrent with AD (see Depression of Alzheimer disease), an early sign of cognitive impairment,^[104] or even the cause.^{[105] [106]}

Diagnostic imaging

When available as a diagnostic tool, single photon emission computed tomography (SPECT) and positron emission tomography (PET) neuroimaging are used to confirm a diagnosis of Alzheimer's in conjunction with evaluations involving mental status examination.^[107] In a person already having dementia, SPECT appears to be superior in differentiating Alzheimer's disease from other possible causes, compared with the usual attempts employing mental testing and medical history analysis.^[108] Advances have led to the proposal of new diagnostic criteria.^{[15] [91]}

A new technique known as PiB PET has been developed for directly and clearly imaging beta-amyloid deposits in vivo using a tracer that binds selectively to the A-beta deposits.^[109] The PiB-PET compound uses carbon-11 PET scanning. Recent studies suggest that PiB-PET is 86% accurate in predicting which people with mild cognitive impairment will develop Alzheimer's disease within two years, and 92% accurate in ruling out the likelihood of developing Alzheimer's.^[110]



A similar PET scanning radiopharmaceutical compound called (E)-4-(2-(6-(2-(2-(2- ^{18}F)-fluoroethoxy)ethoxy)ethoxy)pyridin-3-yl)vinyl)-N-methyl benzenamine, or ^{18}F AV-45, or florbetapir-fluorine-18, or simply florbetapir, contains the longer-lasting radionuclide fluorine-18, has recently been created, and tested as a possible diagnostic tool in Alzheimer's patients.^{[111] [112] [113] [114]} Florbetapir, like PiB, binds to beta-amyloid, but due to its use of fluorine-18 has a half-life of 110 minutes, in contrast to PiB's radioactive half life of 20 minutes. Wong *et al.* found that the longer life allowed the tracer to accumulate significantly more in the brains of the AD patients, particularly in the regions known to be associated with beta-amyloid deposits.^[114]

One review predicted that amyloid imaging is likely to be used in conjunction with other markers rather than as an alternative.^[115]

Volumetric MRI can detect changes in the size of brain regions. Measuring those regions that atrophy during the progress of Alzheimer's disease is showing promise as a diagnostic indicator. It may prove less expensive than other imaging methods currently under study.^[116]

Recent studies suggest that brain metabolite levels may be utilized as biomarkers for Alzheimer's disease.^[117]

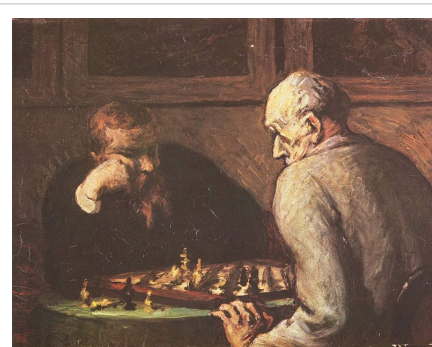
Prevention

At present, there is no definitive evidence to support that any particular measure is effective in preventing AD.^[118] Global studies of measures to prevent or delay the onset of AD have often produced inconsistent results. However, epidemiological studies have proposed relationships between certain modifiable factors, such as diet, cardiovascular risk, pharmaceutical products, or intellectual activities among others, and a population's likelihood of developing AD. Only further research, including clinical trials, will reveal whether these factors can help to prevent AD.^[119]

Although cardiovascular risk factors, such as hypercholesterolemia, hypertension, diabetes, and smoking, are associated with a higher risk of onset and course of AD,^{[120] [121]} statins, which are cholesterol lowering drugs, have not been effective in preventing or improving the course of the disease.^{[122] [123]} The components of a Mediterranean diet, which include fruit and vegetables, bread, wheat and other cereals, olive oil, fish, and red wine, may all individually or together reduce the risk and course of Alzheimer's disease.^[124] Its beneficial cardiovascular effect has been proposed as the mechanism of action.^[124] There is limited evidence that light to moderate use of alcohol, particularly red wine, is associated with lower risk of AD.^[125]

Reviews on the use of vitamins have not found enough evidence of efficacy to recommend vitamin C,^[126] E,^[126] ^[127] or folic acid with or without vitamin B₁₂,^[128] as preventive or treatment agents in AD. Additionally vitamin E is associated with important health risks.^[126] Trials examining folic acid (B9) and other B vitamins failed to show any significant association with cognitive decline.^[129]

Long-term usage of non-steroidal anti-inflammatory drug (NSAIDs) is associated with a reduced likelihood of developing AD.^[130] Human postmortem studies, in animal models, or in vitro investigations also support the notion that NSAIDs can reduce inflammation related to amyloid plaques.^[130] However trials investigating their use as palliative treatment have failed to show positive results while no prevention trial has been completed.^[130] Curcumin from the curry spice turmeric has shown some effectiveness in preventing brain damage in mouse models due to its anti-inflammatory properties.^{[131] [132]} Hormone replacement therapy, although previously used, is no longer thought to prevent dementia and in some cases may even be related to it.^{[133] [134]} There is inconsistent and unconvincing evidence that ginkgo has any positive effect on cognitive impairment and dementia,^[135] and a recent study concludes



Intellectual activities such as playing chess or regular social interaction have been linked to a reduced risk of AD in epidemiological studies, although no causal relationship has been found.

that it has no effect in reducing the rate of AD incidence.^[136] A 21-year study found that coffee drinkers of 3–5 cups per day at midlife had a 65% reduction in risk of dementia in late-life.^[137]

People who engage in intellectual activities such as reading, playing board games, completing crossword puzzles, playing musical instruments, or regular social interaction show a reduced risk for Alzheimer's disease.^[138] This is compatible with the cognitive reserve theory, which states that some life experiences result in more efficient neural functioning providing the individual a cognitive reserve that delays the onset of dementia manifestations.^[138] Education delays the onset of AD syndrome, but is not related to earlier death after diagnosis.^[139] Physical activity is also associated with a reduced risk of AD.^[139]

Some studies have shown an increased risk of developing AD with environmental factors such the intake of metals, particularly aluminium,^{[140] [141]} or exposure to solvents.^[142] The quality of some of these studies has been criticised,^[143] and other studies have concluded that there is no relationship between these environmental factors and the development of AD.^{[144] [145] [146] [147]}

While some studies suggest that Extremely low frequency electromagnetic fields may increase the risk for Alzheimer's disease, reviewers found that further epidemiological and laboratory investigations of this hypothesis are needed.^[148] Smoking is a significant AD risk factor.^[149] Systemic markers of the innate immune system are risk factors for late-onset AD.^[150]

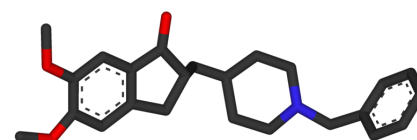
Management

There is no cure for Alzheimer's disease; available treatments offer relatively small symptomatic benefit but remain palliative in nature. Current treatments can be divided into pharmaceutical, psychosocial and caregiving.

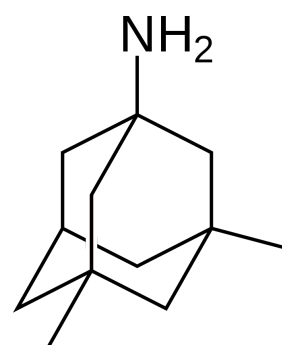
Pharmaceutical

Four medications are currently approved by regulatory agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to treat the cognitive manifestations of AD: three are acetylcholinesterase inhibitors and the other is memantine, an NMDA receptor antagonist. No drug has an indication for delaying or halting the progression of the disease.

Reduction in the activity of the cholinergic neurons is a well-known feature of Alzheimer's disease.^[151] Acetylcholinesterase inhibitors are employed to reduce the rate at which acetylcholine (ACh) is broken down, thereby increasing the concentration of ACh in the brain and combating the loss of ACh caused by the death of cholinergic neurons.^[152] As of 2008, the cholinesterase inhibitors approved for the management of AD symptoms are donepezil (brand name *Aricept*),^[153] galantamine (*Razadyne*),^[154] and rivastigmine (branded as *Exelon*^[155] and *Exelon Patch*^[156]). There is evidence for the efficacy of these medications in mild to moderate Alzheimer's disease,^{[157] [158]} and some evidence for their use in the advanced stage. Only donepezil is approved for treatment of advanced AD dementia.^[159] The use of these drugs in mild cognitive impairment has not shown any effect in a delay of the onset of AD.^[160] The most common side effects are nausea and vomiting, both of which are linked to cholinergic excess. These side



Three-dimensional molecular model of donepezil, an acetylcholinesterase inhibitor used in the treatment of AD symptoms



Molecular structure of memantine, a medication approved for advanced AD symptoms

effects arise in approximately 10–20% of users and are mild to moderate in severity. Less common secondary effects include muscle cramps, decreased heart rate (bradycardia), decreased appetite and weight, and increased gastric acid production.^[161]

Glutamate is a useful excitatory neurotransmitter of the nervous system, although excessive amounts in the brain can lead to cell death through a process called excitotoxicity which consists of the overstimulation of glutamate receptors. Excitotoxicity occurs not only in Alzheimer's disease, but also in other neurological diseases such as Parkinson's disease and multiple sclerosis.^[162] Memantine (brand names *Akatinol*, *Axura*, *Ebixa/Abixa*, *Memox* and *Namenda*),^[163] is a noncompetitive NMDA receptor antagonist first used as an anti-influenza agent. It acts on the glutamatergic system by blocking NMDA receptors and inhibiting their overstimulation by glutamate.^[162] Memantine has been shown to be moderately efficacious in the treatment of moderate to severe Alzheimer's disease. Its effects in the initial stages of AD are unknown.^[164] Reported adverse events with memantine are infrequent and mild, including hallucinations, confusion, dizziness, headache and fatigue.^[165] The combination of memantine and donepezil has been shown to be "of statistically significant but clinically marginal effectiveness".^[166]

Antipsychotic drugs are modestly useful in reducing aggression and psychosis in Alzheimer's patients with behavioural problems, but are associated with serious adverse effects, such as cerebrovascular events, movement difficulties or cognitive decline, that do not permit their routine use.^[167] ^[168] When used in the long-term, they have been shown to associate with increased mortality.^[168]

Medical marijuana appears to be effective in delaying Alzheimer's Disease. The active ingredient in marijuana, THC, prevents the formation of deposits in the brain associated with Alzheimer's disease. THC was found to inhibit acetylcholinesterase more effectively than commercially marketed drugs. THC was also found to delay amylogenesis.^[169] ^[170]

Psychosocial intervention

Psychosocial interventions are used as an adjunct to pharmaceutical treatment and can be classified within behaviour-, emotion-, cognition- or stimulation-oriented approaches. Research on efficacy is unavailable and rarely specific to AD, focusing instead on dementia in general.^[171]

Behavioural interventions attempt to identify and reduce the antecedents and consequences of problem behaviours. This approach has not shown success in improving overall functioning,^[172] but can help to reduce some specific problem behaviours, such as incontinence.^[173] There is a lack of high quality data on the effectiveness of these techniques in other behaviour problems such as wandering.^[174] ^[175]

Emotion-oriented interventions include reminiscence therapy, validation therapy, supportive psychotherapy, sensory integration, also called *snoezelen*, and simulated presence therapy. Supportive psychotherapy has received little or no formal scientific study, but some clinicians find it useful in helping mildly impaired patients adjust to their illness.^[171] Reminiscence therapy (RT) involves the discussion of past experiences individually or in group, many times with the aid of photographs, household items, music and sound recordings, or other familiar items from the past. Although there are few quality studies on the effectiveness of RT, it may be beneficial for cognition and mood.^[176] Simulated presence therapy (SPT) is based on attachment theories and involves playing a recording with voices of the closest relatives of the person with Alzheimer's disease. There is partial evidence indicating that SPT may reduce challenging behaviours.^[177] Finally, validation therapy is based on acceptance of the



A specifically designed room for sensory integration therapy, also called *snoezelen*; an emotion-oriented psychosocial intervention for people with dementia

reality and personal truth of another's experience, while sensory integration is based on exercises aimed to stimulate senses. There is little evidence to support the usefulness of these therapies.^{[178] [179]}

The aim of cognition-oriented treatments, which include reality orientation and cognitive retraining, is the reduction of cognitive deficits. Reality orientation consists in the presentation of information about time, place or person in order to ease the understanding of the person about its surroundings and his or her place in them. On the other hand cognitive retraining tries to improve impaired capacities by exercitation of mental abilities. Both have shown some efficacy improving cognitive capacities,^{[180] [181]} although in some studies these effects were transient and negative effects, such as frustration, have also been reported.^[171]

Stimulation-oriented treatments include art, music and pet therapies, exercise, and any other kind of recreational activities. Stimulation has modest support for improving behaviour, mood, and, to a lesser extent, function. Nevertheless, as important as these effects are, the main support for the use of stimulation therapies is the change in the person's routine.^[171]

Caregiving

Since Alzheimer's has no cure and it gradually renders people incapable of tending for their own needs, caregiving essentially is the treatment and must be carefully managed over the course of the disease.

During the early and moderate stages, modifications to the living environment and lifestyle can increase patient safety and reduce caretaker burden.^{[182] [183]} Examples of such modifications are the adherence to simplified routines, the placing of safety locks, the labelling of household items to cue the person with the disease or the use of modified daily life objects.^{[171] [184] [185]} The patient may also become incapable of feeding themselves, so they require food in smaller pieces or pureed.^[186] When swallowing difficulties arise, the use of feeding tubes may be required. In such cases, the medical efficacy and ethics of continuing feeding is an important consideration of the caregivers and family members.^{[187] [188]} The use of physical restraints is rarely indicated in any stage of the disease, although there are situations when they are necessary to prevent harm to the person with AD or their caregivers.^[171]

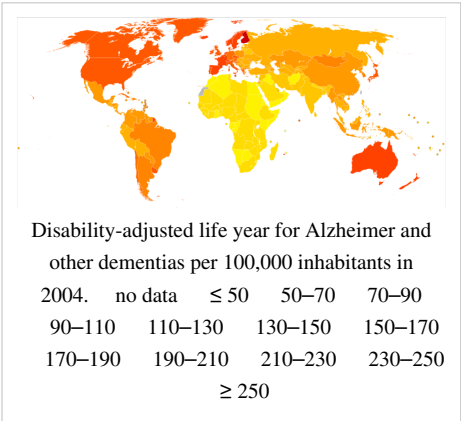
As the disease progresses, different medical issues can appear, such as oral and dental disease, pressure ulcers, malnutrition, hygiene problems, or respiratory, skin, or eye infections. Careful management can prevent them, while professional treatment is needed when they do arise.^{[189] [190]} During the final stages of the disease, treatment is centred on relieving discomfort until death.^[191]

A small recent study in the US concluded that patients whose caregivers had a realistic understanding of the prognosis and clinical complications of late dementia were less likely to receive aggressive treatment near the end of life.^[192]

Prognosis

The early stages of Alzheimer's disease are difficult to diagnose. A definitive diagnosis is usually made once cognitive impairment compromises daily living activities, although the person may still be living independently. The symptoms will progress from mild cognitive problems, such as memory loss through increasing stages of cognitive and non-cognitive disturbances, eliminating any possibility of independent living.^[35]

Life expectancy of the population with the disease is reduced.^{[19] [193] [194]} The mean life expectancy following diagnosis is approximately seven years.^[19] Fewer than 3% of patients live more than fourteen



years.^[20] Disease features significantly associated with reduced survival are an increased severity of cognitive impairment, decreased functional level, history of falls, and disturbances in the neurological examination. Other coincident diseases such as heart problems, diabetes or history of alcohol abuse are also related with shortened survival.^{[193] [195] [196]} While the earlier the age at onset the higher the total survival years, life expectancy is particularly reduced when compared to the healthy population among those who are younger.^[194] Men have a less favourable survival prognosis than women.^{[20] [197]}

The disease is the underlying cause of death in 70% of all cases.^[19] Pneumonia and dehydration are the most frequent immediate causes of death, while cancer is a less frequent cause of death than in the general population.^{[19] [197]}

Epidemiology

Incidence rates
after age 65^[198]

Age	New affected per thousand person–years
65–69	3
70–74	6
75–79	9
80–84	23
85–89	40
90–	69

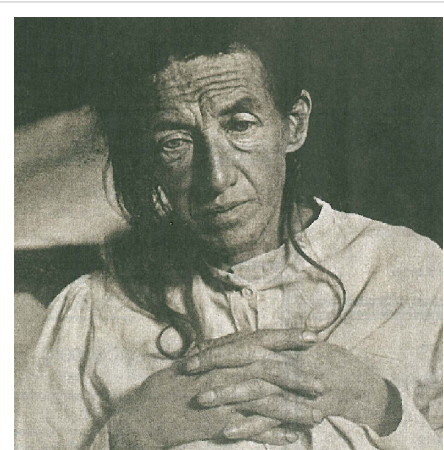
Two main measures are used in epidemiological studies: incidence and prevalence. Incidence is the number of new cases per unit of person–time at risk (usually number of new cases per thousand person–years); while prevalence is the total number of cases of the disease in the population at any given time.

Regarding incidence, cohort longitudinal studies (studies where a disease-free population is followed over the years) provide rates between 10 and 15 per thousand person–years for all dementias and 5–8 for AD,^{[198] [199]} which means that half of new dementia cases each year are AD. Advancing age is a primary risk factor for the disease and incidence rates are not equal for all ages: every five years after the age of 65, the risk of acquiring the disease approximately doubles, increasing from 3 to as much as 69 per thousand person years.^{[198] [199]} There are also sex differences in the incidence rates, women having a higher risk of developing AD particularly in the population older than 85.^{[199] [200]}

Prevalence of AD in populations is dependent upon different factors including incidence and survival. Since the incidence of AD increases with age, it is particularly important to include the mean age of the population of interest. In the United States, Alzheimer prevalence was estimated to be 1.6% in 2000 both overall and in the 65–74 age group, with the rate increasing to 19% in the 75–84 group and to 42% in the greater than 84 group.^[201] Prevalence rates in less developed regions are lower.^[202] The World Health Organization estimated that in 2005, 0.379% of people worldwide had dementia, and that the prevalence would increase to 0.441% in 2015 and to 0.556% in 2030.^[203] Other studies have reached similar conclusions.^[202] Another study estimated that in 2006, 0.40% of the world population (range 0.17–0.89%; absolute number 26.6 million, range 11.4–59.4 million) were afflicted by AD, and that the prevalence rate would triple and the absolute number would quadruple by 2050.^[13]

History

The ancient Greek and Roman philosophers and physicians associated old age with increasing dementia.^[11] It was not until 1901 that German psychiatrist Alois Alzheimer identified the first case of what became known as Alzheimer's disease in a fifty-year-old woman he called Auguste D. Alzheimer followed her until she died in 1906, when he first reported the case publicly.^[204] During the next five years, eleven similar cases were reported in the medical literature, some of them already using the term Alzheimer's disease.^[11] The disease was first described as a distinctive disease by Emil Kraepelin after suppressing some of the clinical (delusions and hallucinations) and pathological features (arteriosclerotic changes) contained in the original report of Auguste D.^[205] He included *Alzheimer's disease*, also named *presenile dementia* by Kraepelin, as a subtype of *senile dementia* in the eighth edition of his *Textbook of Psychiatry*, published in 1910.^[206]



Alois Alzheimer's patient Auguste Deter in 1902. Hers was the first described case of what became known as Alzheimer's disease.

For most of the 20th century, the diagnosis of Alzheimer's disease was reserved for individuals between the ages of 45 and 65 who developed symptoms of dementia. The terminology changed after 1977 when a conference on AD concluded that the clinical and pathological manifestations of presenile and senile dementia were almost identical, although the authors also added that this did not rule out the possibility that they had different causes.^[207] This eventually led to the diagnosis of *Alzheimer's disease* independently of age.^[208] The term *senile dementia of the Alzheimer type* (SDAT) was used for a time to describe the condition in those over 65, with classical Alzheimer's disease being used for those younger. Eventually, the term Alzheimer's disease was formally adopted in medical nomenclature to describe individuals of all ages with a characteristic common symptom pattern, disease course, and neuropathology.^[209]

Society and culture

Social costs

Dementia, and specifically Alzheimer's disease, may be among the most costly diseases for society in Europe and the United States,^[28] ^[29] while their cost in other countries such as Argentina,^[210] or South Korea,^[211] is also high and rising. These costs will probably increase with the ageing of society, becoming an important social problem. AD-associated costs include direct medical costs such as nursing home care, direct nonmedical costs such as in-home day care, and indirect costs such as lost productivity of both patient and caregiver.^[29] Numbers vary between studies but dementia costs worldwide have been calculated around \$160 billion,^[212] while costs of Alzheimer in the United States may be \$100 billion each year.^[29]

The greatest origin of costs for society is the long-term care by health care professionals and particularly institutionalisation, which corresponds to 2/3 of the total costs for society.^[28] The cost of living at home is also very high,^[28] especially when informal costs for the family, such as caregiving time and caregiver's lost earnings, are taken into account.^[213]

Costs increase with dementia severity and the presence of behavioural disturbances,^[214] and are related to the increased caregiving time required for the provision of physical care.^[213] Therefore any treatment that slows cognitive decline, delays institutionalisation or reduces caregivers' hours will have economic benefits. Economic evaluations of current treatments have shown positive results.^[29]

Caregiving burden

The role of the main caregiver is often taken by the spouse or a close relative.^[24] Alzheimer's disease is known for placing a great burden on caregivers which includes social, psychological, physical or economic aspects.^{[25] [26] [27]} Home care is usually preferred by patients and families.^[215] This option also delays or eliminates the need for more professional and costly levels of care.^{[215] [216]} Nevertheless two-thirds of nursing home residents have dementias.^[171]

Dementia caregivers are subject to high rates of physical and mental disorders.^[217] Factors associated with greater psychosocial problems of the primary caregivers include having an affected person at home, the carer being a spouse, demanding behaviours of the cared person such as depression, behavioural disturbances, hallucinations, sleep problems or walking disruptions and social isolation.^{[218] [219]} Regarding economic problems, family caregivers often give up time from work to spend 47 hours per week on average with the person with AD, while the costs of caring for them are high. Direct and indirect costs of caring for an Alzheimer's patient average between \$18,000 and \$77,500 per year in the United States, depending on the study.^{[213] [220]}

Cognitive behavioural therapy and the teaching of coping strategies either individually or in group have demonstrated their efficacy in improving caregivers' psychological health.^{[25] [221]}

Notable cases

As Alzheimer's disease is highly prevalent, many notable people have developed it. Well-known examples are former United States President Ronald Reagan and Irish writer Iris Murdoch, both of whom were the subjects of scientific articles examining how their cognitive capacities deteriorated with the disease.^{[222] [223] [224]} Other cases include the retired footballer Ferenc Puskas,^[225] the former Prime Ministers Harold Wilson (United Kingdom) and Adolfo Suárez (Spain),^{[226] [227]} the actress Rita Hayworth,^[228] the actor Charlton Heston,^[229] the novelist Terry Pratchett,^[230] and the 2009 Nobel Prize in Physics recipient Charles K. Kao.^[231]



Charlton Heston and Ronald Reagan at a meeting in the White House. Both of them would later develop Alzheimer's disease.

AD has also been portrayed in films such as: *Iris* (2001),^[232] based on John Bayley's memoir of his wife Iris Murdoch,^[233] *The Notebook* (2004),^[234] based on Nicholas Sparks' 1996 novel of the same name,^[235] *A Moment to Remember* (2004);^[236] *Thanmathra* (2005);^[236] *Memories of Tomorrow* (*Ashita no Kioku*) (2006),^[237] based on Hiroshi Ogiwara's novel of the same name,^[238] *Away from Her* (2006), based on Alice Munro's short story "The Bear Came over the Mountain".^[239] Documentaries on Alzheimer's disease include *Malcolm and Barbara: A Love Story* (1999) and *Malcolm and Barbara: Love's Farewell* (2007), both featuring Malcolm Pointon.^[240]

Research directions

As of 2008, the safety and efficacy of more than 400 pharmaceutical treatments are being investigated in clinical trials worldwide, and approximately a quarter of these compounds are in Phase III trials; the last step prior to review by regulatory agencies.^[241]

One area of clinical research is focused on treating the underlying disease pathology. Reduction of amyloid beta levels is a common target of compounds^[242] (such as apomorphine) under investigation. Immunotherapy or vaccination for the amyloid protein is one treatment modality under study.^[243] Unlike preventative vaccination, the putative therapy would be used to treat people already diagnosed. It is based upon the concept of training the immune system to recognise, attack, and reverse deposition of amyloid, thereby altering the course of the disease.^[244] An example of such a vaccine under investigation was ACC-001,^{[245] [246]} although the trials were

suspended in 2008.^[247] Another similar agent is bapineuzumab, an antibody designed as identical to the naturally induced anti-amyloid antibody.^[248] Other approaches are neuroprotective agents, such as AL-108,^[249] and metal-protein interaction attenuation agents, such as PBT2.^[250] A TNF α receptor fusion protein, etanercept has showed encouraging results.^[251]

In 2008, two separate clinical trials showed positive results in modifying the course of disease in mild to moderate AD with methylthioninium chloride (trade name *rember*), a drug that inhibits tau aggregation,^[252] ^[253] and dimebon, an antihistamine.^[254] The consecutive Phase-III trial of Dimebon failed to show positive effects in the primary and secondary endpoints.^[255]

The possibility that AD could be treated with antiviral medication is suggested by a study showing colocation of herpes simplex virus with amyloid plaques.^[256]

Preliminary research on the effects of meditation on retrieving memory and cognitive functions have been encouraging. Limitations of this research can be addressed in future studies with more detailed analyses.^[257]

See also

- Art and dementia

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Further reading

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- *Can Alzheimer's Disease Be Prevented?* (<http://www.nia.nih.gov/Alzheimers/Publications/ADPrevented/>). US Department of Health and Human Services, National Institute on Aging, NIH. 2009.
- *Caring for a Person with Alzheimer's Disease: Your Easy-to-Use Guide from the National Institute on Aging* (<http://www.nia.nih.gov/Alzheimers/Publications/CaringAD/>). US Department of Health and Human Services, National Institute on Aging, NIH. 2009.
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External links

- Alzheimer's Disease Centers (ADCs) (<http://www.nia.nih.gov/Alzheimers/ResearchInformation/ResearchCenters/>)
- Alzheimer's Disease Education and Referral (ADEAR) Center (<http://www.nia.nih.gov/alzheimers>)
- Alzheimer's Association (<http://www.alz.org/index.asp>)
- UCSF Memory and Aging Center (<http://memory.ucsf.edu/>)

2D-FT NMR and Nuclear Magnetic Resonance Imaging

2D-FT Nuclear Magnetic resonance imaging

(2D-FT NMRI), or **Two-dimensional Fourier transform magnetic resonance imaging (NMRI)**, is primarily a non-invasive imaging technique most commonly used in biomedical research and medical radiology/ nuclear medicine to visualize structures and functions of the living systems and single cells. For example it can provides fairly detailed images of a human body in any selected cross-sectional plane, such as longitudinal, transversal, sagittal, etc. NMRI provides much greater contrast especially for the different soft tissues of the body than computed tomography (CT) as its most sensitive option observes the nuclear spin distribution and dynamics of highly mobile molecules that contain the naturally abundant, stable hydrogen isotope ^1H as in plasma water molecules, blood, dissolved metabolites and fats. This approach makes it most useful in cardiovascular, oncological (cancer), neurological (brain), musculoskeletal, and cartilage imaging. Unlike CT, it uses no ionizing radiation, and also unlike nuclear imaging it does not employ any radioactive isotopes. Some of the first MRI images reported were published in 1973^[1] and the first study performed on a human took place on July 3, 1977.^[2] Earlier papers were also published by Peter Mansfield in UK (Nobel Laureate in 2007, and R. Damadian in the USA, (together with an approved patent for magnetic imaging). Unpublished 'high-resolution' (50 micron resolution) images of other living systems, such as hydrated wheat grains, were obtained and communicated in UK in 1977-1979, and were subsequently confirmed by articles published in *Nature*.

NMRI Principle

Certain nuclei such as ^1H nuclei, or 'fermions' have spin-1/2, because there are two spin states, referred to as "up" and "down" states. The nuclear magnetic resonance absorption phenomenon occurs when samples containing such nuclear spins are placed in a static magnetic field and a very short radiofrequency pulse is applied with a center, or carrier, frequency matching that of the transition between the up and down states of the spin-1/2 ^1H nuclei that were polarized by the static magnetic field.



Modern 3 tesla clinical MRI scanner.

A number of methods have been devised for combining magnetic field gradients and radiofrequency pulsed excitation to obtain an image. Two major methods involve either 2D-FT or 3D-FT reconstruction from projections, somewhat similar to Computed Tomography, with the exception of the image interpretation that in the former case must include dynamic and relaxation/contrast enhancement information as well. Other schemes involve building the NMR image either point-by-point or line-by-line. Some schemes use instead gradients in the rf field rather than in the static magnetic field. The majority of NMR images routinely obtained are either by the Two-Dimensional Fourier Transform (2D-FT) technique (with slice selection), or by the Three-Dimensional Fourier Transform (3D-FT) techniques that are however much more time consuming at present. 2D-FT NMRI is sometime called in common parlance a "spin-warp". An NMR image corresponds to a spectrum consisting of a number of 'spatial frequencies' at different locations in the sample investigated, or in a patient. A two-dimensional Fourier transformation of such a "real" image may be considered as a representation of such "real waves" by a matrix of spatial frequencies known as the k -space. We shall see next in some mathematical detail how the 2D-FT computation works to obtain 2D-FT NMR images.

Two-dimensional Fourier transform imaging

A two-dimensional Fourier transform (2D-FT) is computed numerically or carried out in two stages, both involving 'standard', one-dimensional Fourier transforms. However, the second stage Fourier transform is not the inverse Fourier transform (which would result in the original function that was transformed at the first stage), but a Fourier transform in a second variable-- which is 'shifted' in value-- relative to that involved in the result of the first Fourier transform. Such 2D-FT analysis is a very powerful method for three-dimensional reconstruction of polymer and biopolymer structures by two-dimensional Nuclear Magnetic Resonance (Kurt Wutrich 1986: 2D-FT NMR of solutions ^[3]) for molecular weights (Mw) of the dissolved polymers up to about 50,000 Mw. For larger biopolymers or polymers, more complex methods have been developed to obtain the desired resolution needed for the 3D-reconstruction of higher molecular structures, e.g. for 900,000 Mw, methods that can also be utilized *in vivo*. The 2D-FT method is also widely utilized in optical spectroscopy, such as *2D-FT NIR hyperspectral imaging*, or in MRI imaging for research and clinical, diagnostic applications in Medicine. A more precise mathematical definition of the 'double' Fourier transform involved is specified next, and a precise example follows the definition. A *2D-FT, or two-dimensional Fourier transform*, is a standard Fourier transformation of a function of two variables, $f(x_1, x_2)$, carried first in the first variable x_1 , followed by the Fourier transform in the second variable x_2 of the resulting function $F(s_1, x_2)$.

Example 1

A 2D Fourier transformation and phase correction is applied to a set of 2D NMR (FID) signals : $s(t_1, t_2)$ yielding a real 2D-FT NMR 'spectrum' (collection of 1D FT-NMR spectra) represented by a matrix S whose elements are

$$S(\nu_1, \nu_2) = \text{Re} \int \int \cos(\nu_1 t_1) \exp(-i\nu_2 t_2) s(t_1, t_2) dt_1 dt_2$$

where : ν_1 and : ν_2 denote the discrete indirect double-quantum and single-quantum(detection) axes, respectively, in the 2D NMR experiments. Next, the $\text{\textbackslash emph\{covariance matrix\}}$ is calculated in the frequency domain according to the following equation

$$C(\nu'_2, \nu_2) = S^T S = \sum_{\nu_1} [S(\nu_1, \nu'_2) S(\nu_1, \nu_2)], \text{ with : } \nu_2, \nu'_2 \text{ taking all possible single-quantum}$$

frequency values and with the summation carried out over all discrete, double quantum frequencies : ν_1 .

Example 2

2D-FT STEM Images ^[4] (obtained at Cornell University) of electron distributions in a high-temperature cuprate superconductor 'paracrystal' reveal both the domains (or 'location') and the local symmetry of the 'pseudo-gap' in the electron-pair correlation band responsible for the high-temperature superconductivity effect (maybe a possible, next Nobel if and only if the mathematical physics treatment is also developed to include also such results). So far there have been three Nobel prizes awarded for 2D-FT NMR/MRI during 1992-2003, and an additional, earlier Nobel prize for 2D-FT of X-ray data ('CAT scans'); recently the advanced possibilities of 2D-FT techniques in Chemistry, Physiology and Medicine ^[5] received very significant recognition.

Brief explanation of NMRI Diagnostic Uses in Pathology

As an example, a diseased tissue, such as that inside tumors, can be detected because the hydrogen nuclei of molecules in different tissues return to their equilibrium spin state at different relaxation rates. By changing the pulse delays in the RF pulse sequence employed, and or the pulse sequence itself one may obtain a 'relaxation-based contrast' between different types of body tissue, such as normal vs. diseased tissue cells for example. Excluded from such diagnostic observations by NMRI are all patients with some metal implants, cochlear implants, and all cardiac pacemaker patients who cannot undergo any NMRI scan because of the very intense magnetic and rf fields employed in NMRI. It is conceivable that future developments may also include along with the NMRI diagnostic treatments with special techniques involving applied magnetic fields and very high frequency RF. Already, surgery with special tools is being experimented on in the presence of NMR imaging of subjects. Thus, NMRI is used to image almost every part of the body, and is especially useful in neurological conditions, disorders of the muscles and joints, for evaluating tumors, such as in lung or skin cancers, abnormalities in the heart (especially in children with hereditary disorders), blood vessels, CAD and atherosclerosis.

See also

- Earth's field NMR (EFNMR)
- Magnetic resonance microscopy
- Nuclear magnetic resonance (NMR)
- Medical imaging
- Magnetic resonance elastography
- Relaxation
- Robinson oscillator

Footnotes

- [1] Lauterbur, P.C., Nobel Laureate in 2003 (1973). "Image Formation by Induced Local Interactions: Examples of Employing Nuclear Magnetic Resonance". *Nature* **242**: 190–1. doi:10.1038/242190a0.
- [2] [<http://www.howstuffworks.com/mri.htm/printable>] Howstuffworks "How MRI Works"
- [3] http://en.wikipedia.org/wiki/Nuclear_magnetic_resonance#Nuclear_spin_and_magnets
- [4] http://74.125.95.132/search?q=cache:x6OQWq_GVoYJ:www.physorg.com/multimedia/pix1815/+http://www.physorg.com/multimedia/pix1815/&hl=en&ct=clnk&cd=1&gl=uk
- [5] http://nobelprize.org/nobel_prizes/chemistry/laureates/1991/ernst-lecture.pdf

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- 2D-FT NMRI Instrument example: A JPG color image of a 2D-FT NMR Imaging 'monster' Instrument (<http://upload.wikimedia.org/wikipedia/en/b/bf/HWB-NMRv900.jpg>).
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- Paul Lauterbur. 2003. Nobel Laureate in Physiology and Medicine for (2D and 3D) MRI. (http://nobelprize.org/nobel_prizes/medicine/laureates/2003/)
- Jean Jeener. 1971. Two-dimensional Fourier Transform NMR, presented at an Ampere International Summer School, Basko Polje, unpublished. A verbatim quote follows from Richard R. Ernst's Nobel Laureate Lecture delivered on December 2nd, 1992, "A new approach to measure two-dimensional (2D) spectra." has been proposed by Jean Jeener at an Ampere Summer School in Basko Polje, Yugoslavia, 1971 (Jean Jeener, 1971). He suggested a 2D Fourier transform experiment consisting of two $\pi/2$ pulses with a variable time t_1 between the pulses and the time variable t_2 measuring the time elapsed after the second pulse as shown in Fig. 6 that expands the principles of Fig. 1. Measuring the response $S(t_1, t_2)$ of the two-pulse sequence and Fourier-transformation with respect to both time variables produces a two-dimensional spectrum $S(O_1, O_2)$ of the desired form. This two-pulse experiment by Jean Jeener is the forefather of a whole class of 2D experiments that can also easily be expanded to multidimensional spectroscopy.
- Haacke, E Mark; Brown, Robert F; Thompson, Michael; Venkatesan, Ramesh (1999). *Magnetic resonance imaging: physical principles and sequence design*. New York: J. Wiley & Sons. ISBN 0-471-35128-8.

External links

- 3D Animation Movie about MRI Exam (<http://www.patencys.com/MRI/>)
- Interactive Flash Animation on MRI (<http://www.e-mri.org>) - *Online Magnetic Resonance Imaging physics and technique course*
- International Society for Magnetic Resonance in Medicine (<http://www.ismrm.org>)
- Danger of objects flying into the scanner (http://www.simplyphysics.com/flying_objects.html)

See also

- Earth's field NMR (EFNMR)
- Medical imaging
- Magnetic resonance microscopy
- Magnetic resonance elastography
- Nuclear magnetic resonance (NMR)
- Relaxation
- Robinson oscillator
- Rabi cycle

[[Category:Magnetic resonance imaging|]] [[Category:Medical imaging]] [[Category:1973 introductions]] {{Link FAleu}} {{Link FAIsk}} {{Link FAIzh}} [[ar:إيسينغمانغمالا نينرلاب ريوصت]] [[cs:Magnetická rezonance]] [[de:Magnetresonanztomographie]] [[et:Magnetresonantsomograafia]] [[el:Μαγνητική τομογραφία]] [[es:Resonancia magnética]] [[eo:Magneta resonanca bildigo]] [[eu:Erresonantzia Magnetiko bidezko Irudigintza]] [[fa:آرام]] [[fr:Imagerie par résonance magnétique]] [[hr:Magnetna rezonancija]] [[id:MRI]] [[it:Imaging a risonanza magnetica]] [[he:דמית המגנטית]] [[lb:Magnéitresonanztomographie]] [[hu:MRI]] [[ms:MRI]] [[nl:MRI-scanner]] [[ja:核磁気共鳴画像法]] [[no:Magnetresonanstomografi]] [[nn:Magnetresonanstomografi]] [[pl:Obrazowanie rezonansu magnetycznego]] [[pt:Ressonância magnética]] [[ru:Магнитно-резонансная томография]] [[simple:Magnetic resonance imaging]] [[sk:Zobrazovanie magnetickou rezonanciou]] [[sl:Slikanje z magnetno resonanco]] [[fi:Magneettikuvaus]] [[sv:Magnetisk resonanstomografi]] [[th:การสร้างภาพด้วยเรโซแนนซ์แม่เหล็ก]] [[vi:Chụp cộng hưởng từ]] [[zh:核磁共振成像]]

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Cancer screening

Cancer screening occurs for many type of cancer including breast, prostate, lung, and colorectal cancer. Cancer screening is an attempt to detect unsuspected cancers in an asymptomatic population.

Screening tests suitable for large numbers of apparently healthy people must be relatively affordable, safe, noninvasive procedures with acceptably low rates of false positive results. If signs of cancer are detected, more definitive and invasive follow-up tests are performed to confirm the diagnosis.

Screening for cancer can lead to earlier diagnosis in specific cases. Early diagnosis may lead to higher rates of successful treatment and extended life. However, it may also falsely appear to prolong the lead time to death through lead time bias or length time bias.

Types of screening

A number of different screening tests have been developed for different malignancies. Breast cancer screening can be done by breast self-examination, though this approach was discredited by a 2005 study in over 300,000 Chinese women. Screening for breast cancer with mammograms has been shown to reduce the average stage of diagnosis of breast cancer in a population. Stage of diagnosis in a country has been shown to decrease within ten years of introduction of mammographic screening programs. Colorectal cancer can be detected through fecal occult blood testing [1] and colonoscopy, which reduces both colon cancer incidence and mortality, presumably through the detection and removal of pre-malignant polyps. Similarly, cervical cytology testing (using the Pap smear) leads to the identification and excision of precancerous lesions. Over time, such testing has been followed by a dramatic reduction of cervical cancer incidence and mortality. Testicular self-examination is recommended for men beginning at the age of 15 years to detect testicular cancer. Prostate cancer can be screened using a digital rectal exam along with prostate specific antigen (PSA) blood testing, though some authorities (such as the US Preventive Services Task Force) recommend against routinely screening all men.

Risks and benefits

Screening for cancer is controversial in cases when it is not yet known if the test actually saves lives. Screening can lead to substantial false positive result and subsequent invasive procedures.^[2] The controversy arises when it is not clear if the benefits of screening outweigh the risks of follow-up diagnostic tests and cancer treatments. Cancer screening is not indicated unless life expectancy is greater than five years and the benefit is uncertain over the age of 70.^[3]

Prostate cancer

When screening for prostate cancer, the PSA test may detect small cancers that would never become life threatening, but once detected will lead to treatment. This situation, called overdiagnosis, puts men at risk for complications from unnecessary treatment such as surgery or radiation. Follow up procedures used to diagnose prostate cancer (prostate biopsy) may cause side effects, including bleeding and infection. Prostate cancer treatment may cause incontinence (inability to control urine flow) and erectile dysfunction (erections inadequate for intercourse).

Breast cancer

Similarly, for breast cancer, there have recently been criticisms that breast screening programs in some countries cause more problems than they solve. This is because screening of women in the general population will result in a large number of women with false positive results which require extensive follow-up investigations to exclude cancer, leading to having a high number-to-treat (or number-to-screen) to prevent or catch a single case of breast cancer early.

Cervical cancer

Cervical cancer screening via the Pap smear has the best cost-benefit profile of all the forms of cancer screening from a public health perspective as, being largely caused by a virus, it has clear risk factors (sexual contact), and the natural progression of cervical cancer is that it normally spreads slowly over a number of years therefore giving more time for the screening program to catch it early. Moreover, the test itself is easy to perform and relatively cheap.

Medical imaging

Use of medical imaging to search for cancer in people without clear symptoms is similarly marred with problems. There is a significant risk of detection of what has been recently called an *incidentaloma* - a benign lesion that may be interpreted as a malignancy and be subjected to potentially dangerous investigations. Recent studies of CT scan-based screening for lung cancer in smokers have had equivocal results, and systematic screening is not recommended as of July 2007. Randomized clinical trials of plain-film chest X-rays to screen for lung cancer in smokers have shown no benefit for this approach.

See also

- Overdiagnosis
- Type I and type II errors
- Epidemiology of cancer

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- [2] Croswell JM, Kramer BS, Kreimer AR, *et al.* (2009). "Cumulative incidence of false-positive results in repeated, multimodal cancer screening" (<http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=2682972>). *Ann Fam Med* **7** (3): 212–22. doi:10.1370/afm.942. PMID 19433838. PMC 2682972.
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- Aziz, Khalid; George Y. Wu (2002). *Cancer screening: a practical guide for physicians* (<http://www.springer.com/humana+press/book/978-0-89603-865-3>). Current Clinical Practice. Humana Press. pp. 324. ISBN 0896038653.

External links

- NHS cancer screening programmes (<http://www.cancerscreening.nhs.uk/>)
- Screening for cancer (<http://www.cancerhelp.org.uk/help/default.asp?page=106>), Cancer Research UK
- Cancer screening overview (<http://www.cancer.gov/cancertopics/pdq/screening/overview/healthprofessional>), National Cancer Institute
- Cancer Screening (<http://www.emedicinehealth.com/script/main/art.asp?articlekey=60167>), eMedicineHealth
- ColonCancerCheck (<http://www.coloncancercheck.ca/>) including fact sheets in 24 languages at Ontario Ministry of Health and Long-Term Care

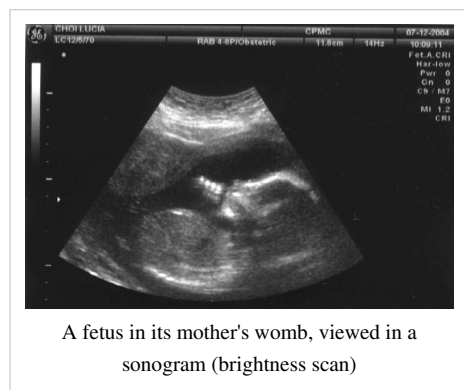
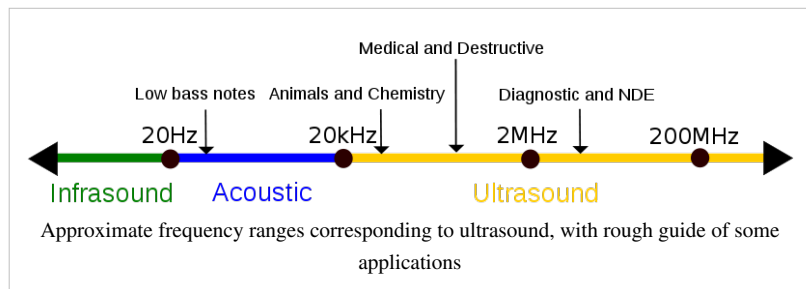
Ultrasound Imaging

Ultrasound is cyclic sound pressure with a frequency greater than the upper limit of human hearing. Although this limit varies from person to person, it is approximately 20 kilohertz (20,000 hertz) in healthy, young adults and thus, 20 kHz serves as a useful lower limit in describing ultrasound. The production of ultrasound is used in many different fields, typically to penetrate a medium and measure the reflection signature or supply focused energy. The reflection signature can reveal details about the inner structure of the medium, a property also used by animals such as bats for hunting. The most well known application of ultrasound is its use in sonography to produce pictures of fetuses in the human womb. There are a vast number of other applications as well.^[1]

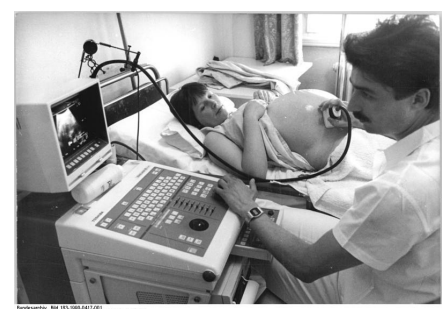
Ability to hear ultrasound

The upper frequency limit in humans (approximately 20 kHz) is due to limitations of the middle ear, which acts as a low-pass filter. Ultrasonic hearing can occur if ultrasound is fed directly into the skull bone and reaches the cochlea through bone conduction without passing through the middle ear.

It is a fact in psychoacoustics that children can hear some high-pitched sounds that older adults cannot hear, because in humans the upper limit pitch of hearing tends to become lower with age.^[2] A cell phone company has used this to create ring signals supposedly only able to be heard by younger humans,^[3] but many older people are able to hear it, which may be due to the considerable variation of age-related deterioration in the upper hearing threshold.



Some animals — such as dogs, cats, dolphins, bats, and mice — have an upper frequency limit that is greater than that of the human ear and thus can hear ultrasound, which is how a dog whistle works.



An ultrasound examination in East Germany, 1990

Diagnostic sonography

Medical sonography (ultrasonography) is an ultrasound-based diagnostic medical imaging technique used to visualize muscles, tendons, and many internal organs, to capture their size, structure and any pathological lesions with real time tomographic images. Ultrasound has been used by radiologists and sonographers to image the human body for at least 50 years and has become one of the most widely used diagnostic tools in modern medicine. The technology is relatively inexpensive and portable, especially when compared with other techniques, such as magnetic resonance imaging (MRI) and computed tomography (CT). Ultrasound is also used to visualize fetuses during routine and emergency prenatal care. Such diagnostic applications used during pregnancy are referred to as obstetric sonography.

As currently applied in the medical field, properly performed ultrasound poses no known risks to the patient.^[4] Sonography is generally described as a "safe test" because it does not use mutagenic ionizing radiation, which can pose hazards such as chromosome breakage and cancer development. However, ultrasonic energy has two potential physiological effects: it enhances inflammatory response; and it can heat soft tissue. Ultrasound energy produces a mechanical pressure wave through soft tissue. This pressure wave may cause microscopic bubbles in living tissues and distortion of the cell membrane, influencing ion fluxes and intracellular activity. When ultrasound enters the body, it causes molecular friction and heats the tissues slightly. This effect is typically very minor as normal tissue perfusion dissipates most of the heat, but with high intensity, it can also cause small pockets of gas in body fluids or tissues to expand and contract/collapse in a phenomenon called cavitation; however this is not known to occur at diagnostic power levels used by modern diagnostic ultrasound units.

In 2008, the AIUM published a 130-page report titled "American Institute of Ultrasound in Medicine Consensus Report on Potential Bioeffects of Diagnostic Ultrasound"^[5] stating that there are indeed some potential risks to



Sonogram of a fetus at 14 weeks (profile)



Head of a fetus, aged 29 weeks, in a "3D ultrasound"

administering ultrasound tests, which include "postnatal thermal effects, fetal thermal effects, postnatal mechanical effects, fetal mechanical effects, and bioeffects considerations for ultrasound contrast agents."^[6] The long-term effects of tissue heating and cavitation have shown decreases in the size of red blood cells in cattle when exposed to intensities higher than diagnostic levels.^[7] However, long term effects due to ultrasound exposure at diagnostic intensity is still unknown.^[8]

There are several studies that indicate the harmful side effects on animal fetuses associated with the use of sonography on pregnant mammals. A Yale study in 2006 suggested exposure to ultrasound affects fetal brain development in mice. A typical fetal scan, including evaluation for fetal malformations, typically takes 10–30 minutes.^[9] The study showed that rodent brain cells failed to migrate to their proper positions and remained scattered in incorrect parts of the brain. This misplacement of brain cells during their development is linked to disorders ranging from "mental retardation and childhood epilepsy to developmental dyslexia, autism spectrum disorders and schizophrenia." However, this effect was only detectable after 30 minutes of continuous scanning. No link has yet been made between the test results on animals such as mice and the possible effects on humans. Although the possibility exists that biological effects on humans may be identified in the future, currently most doctors feel that based on available information the benefits to patients outweigh the risks.^[10] Also the ALARA (As Low As Reasonably Achievable) principle has been advocated for an ultrasound examination; that is keeping the scanning time and power settings as low as possible but consistent with diagnostic imaging; and that is the principle by which non-medical uses which by definition are not necessary are actively discouraged.

Obstetric ultrasound can be used to identify many conditions that would be harmful to the mother and the baby. Many health care professionals consider the risk of leaving these conditions undiagnosed to be much greater than the very small risk, if any, associated with undergoing an ultrasound scan. According to Cochrane Review, routine ultrasound in early pregnancy (less than 24 weeks) appears to enable better gestational age assessment, earlier detection of multiple pregnancies and earlier detection of clinically unsuspected fetal malformation at a time when termination of pregnancy is possible.^[11]

Sonography is used routinely in obstetric appointments during pregnancy, but the FDA discourages its use for non-medical purposes such as fetal keepsake videos and photos, even though it is the same technology used in hospitals.^[12]

Obstetric ultrasound is primarily used to:

- Date the pregnancy (gestational age)
- Confirm fetal viability
- Determine location of fetus, intrauterine vs ectopic
- Check the location of the placenta in relation to the cervix
- Check for the number of fetuses (multiple pregnancy)
- Check for major physical abnormalities.
- Assess fetal growth (for evidence of intrauterine growth restriction (IUGR))
- Check for fetal movement and heartbeat.
- Determine the sex of the baby

Unfortunately, results are occasionally wrong, producing a false positive (the Cochrane Collaboration is a relevant effort to improve the reliability of health care trials). False detection may result in patients being warned of birth defects when no such defect exists. Sex determination is only accurate after 12 weeks gestation. When balancing risk and reward, there are recommendations to avoid the use of routine ultrasound for low risk pregnancies. In many countries ultrasound is used routinely in the management of all pregnancies.

According to the European Committee of Medical Ultrasound Safety (ECMUS) "Ultrasonic examinations should only be performed by competent personnel who are trained and updated in safety matters. Ultrasound produces heating, pressure changes and mechanical disturbances in tissue. Diagnostic levels of ultrasound can produce temperature rises that are hazardous to sensitive organs and the embryo/fetus. Biological effects of non-thermal

origin have been reported in animals but, to date, no such effects have been demonstrated in humans, except when a microbubble contrast agent is present."^[13] Nonetheless, care should be taken to use low power settings and avoid pulsed wave scanning of the fetal brain unless specifically indicated in high risk pregnancies.

It should be noted that obstetrics is not the only use of ultrasound. Soft tissue imaging of many other parts of the body is conducted with ultrasound. Other scans routinely conducted are cardiac, renal, liver and gallbladder (hepatic). Other common applications include musculo-skeletal imaging of muscles, ligaments and tendons, ophthalmic ultrasound (eye) scans and superficial structures such as testicle, thyroid, salivary glands and lymph nodes. Because of the real time nature of ultrasound, it is often used to guide interventional procedures such as fine needle aspiration FNA or biopsy of masses for cytology or histology testing in the breast, thyroid, liver, kidney, lymph nodes, muscles and joints.

Ultrasound scanners have different Doppler-techniques to visualize arteries and veins. The most common is colour doppler or power doppler, but also other techniques like b-flow are used to show bloodflow in an organ. By using pulsed wave doppler or continuous wave doppler bloodflow velocities can be calculated.

Figures released for the period 2005-2006 by UK Government (Department of Health) show that non-obstetric ultrasound examinations constituted more than 65% of the total number of ultrasound scans conducted.

Ultrasound is also increasingly being used in trauma and first aid cases, with emergency ultrasound becoming a staple of most EMT response teams.

Biomedical ultrasonic applications

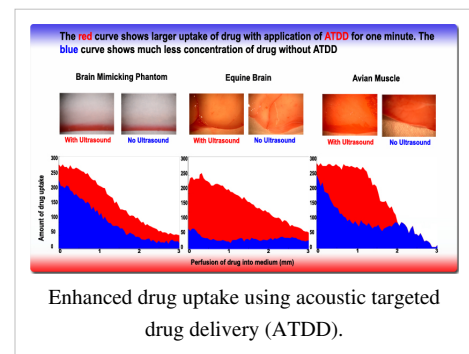
Ultrasound also has therapeutic applications, which can be highly beneficial when used with dosage precautions.^[14]

- According to RadiologyInfo,^[15] ultrasounds are useful in the detection of pelvic abnormalities and can involve techniques known as abdominal (transabdominal) ultrasound, vaginal (transvaginal or endovaginal) ultrasound in women, and also rectal (transrectal) ultrasound in men.
- Focused high-energy ultrasound pulses can be used to break calculi such as kidney stones and gallstones into fragments small enough to be passed from the body without undue difficulty, a process known as lithotripsy.
- Treating benign and malignant tumors and other disorders via a process known as high intensity focused ultrasound (HIFU), also called *focused ultrasound surgery* (FUS). In this procedure, a generally lower frequencies than medical diagnostic ultrasound is used (250–2000 kHz), but significantly higher time-averaged intensities. The treatment is often guided by magnetic resonance imaging (MRI)—this is called *Magnetic resonance-guided focused ultrasound* (MRgFUS). Delivering chemotherapy to brain cancer cells and various drugs to other tissues is called acoustic targeted drug delivery (ATDD).^[16] These procedures generally use high frequency ultrasound (1-10 MHz) and a range of intensities (0-20 watts/cm²). The acoustic energy is focused on the tissue of interest to agitate its matrix and make it more permeable for therapeutic drugs.^{[17] [18]}

- Therapeutic ultrasound, a technique that uses more powerful ultrasound sources to generate cellular effects in soft tissue has fallen out of favor as research has shown a lack of efficacy^[19] and a lack of scientific basis for proposed biophysical effects.^[20]

Ultrasound has been used in cancer treatment.

- Cleaning teeth in dental hygiene.
- Focused ultrasound sources may be used for cataract treatment by phacoemulsification.
- Additional physiological effects of low-intensity ultrasound have recently been discovered, e.g. the ability to stimulate bone-growth and its potential to disrupt the blood-brain barrier for drug delivery.

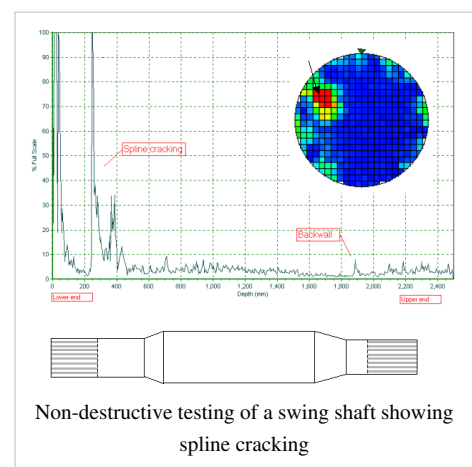


- Ultrasound is essential to the procedures of ultrasound-guided sclerotherapy and endovenous laser treatment for the non-surgical treatment of varicose veins.
- Ultrasound-assisted lipectomy is lipectomy assisted by ultrasound. Liposuction can also be assisted by ultrasound.
- Doppler ultrasound is being tested for use in aiding tissue plasminogen activator treatment in stroke sufferers in the procedure called ultrasound-enhanced systemic thrombolysis.
- Low intensity pulsed ultrasound is used for therapeutic tooth and bone regeneration.
- Ultrasound can also be used for elastography. This can be useful in medical diagnoses, as elasticity can discern healthy from unhealthy tissue for specific organs/growths. In some cases unhealthy tissue may have a lower system Q, meaning that the system acts more like a large heavy spring as compared to higher values of system Q (healthy tissue) that respond to higher forcing frequencies. Ultrasonic elastography is different from conventional ultrasound, as a transceiver (pair) and a transmitter are used instead of only a transceiver. One transducer acts as both the transmitter and receiver to image the region of interest over time. The extra transmitter is a very low frequency transmitter, and perturbs the system so the unhealthy tissue oscillates at a low frequency and the healthy tissue does not. The transceiver, which operates at a high frequency (typically MHz) then measures the displacement of the unhealthy tissue (oscillating at a much lower frequency). The movement of the slowly oscillating tissue is used to determine the elasticity of the material, which can then be used to distinguish healthy tissue from the unhealthy tissue.
- Ultrasound has been shown to act synergistically with antibiotics in bacterial cell killing.^[21]
- Ultrasound has been postulated to allow thicker eukaryotic cell tissue cultures by promoting nutrient penetration.^[22]
- Ultrasound in the low MHz range in the form of standing waves is an emerging tool for contactless separation, concentration and manipulation of microparticles and biological cells, a method referred to as acoustophoresis. The basis is the acoustic radiation force, a non-linear effect which causes particles to be attracted to either the nodes or anti-nodes of the standing wave depending on the acoustic contrast factor, which is a function of the sound velocities and densities of the particle and of the medium in which the particle is immersed.
- Ultrasound laboratory research based on clinically diagnostic systems is a popular way of making use of a real-time, lower cost (in comparison to MRI and CT) imaging modality for study of biomedical applications and image processing techniques. The ultrasound research interface is a tool that bridges the gap between useful laboratory equipment and a clinical device, and can be used to collect raw data for external or real-time analysis using special algorithms and protocols.

Industrial ultrasound

Ultrasonic testing is a type of nondestructive testing commonly used to find flaws in materials and to measure the thickness of objects. Frequencies of 2 to 10 MHz are common but for special purposes other frequencies are used. Inspection may be manual or automated and is an essential part of modern manufacturing processes. Most metals can be inspected as well as plastics and aerospace composites. Lower frequency ultrasound (50–500 kHz) can also be used to inspect less dense materials such as wood, concrete and cement.

Ultrasound can also be used for heat transfer in liquids. Researchers recently employed ultrasound in dry corn milling plant to enhance ethanol production.^[23]



Ultrasonic manipulation and characterization of particles

A researcher at the Industrial Materials Research Institute, Alessandro Malutta, devised an experiment that demonstrated the trapping action of ultrasonic standing waves on wood pulp fibers diluted in water and their parallel orienting into the equidistant pressure planes.^[24] The time to orient the fibers in equidistant planes is measured with a laser and an electro-optical sensor. This could provide the paper industry a quick on-line fiber size measurement system. A somewhat different implementation was demonstrated at Penn State University using a microchip which generated a pair of perpendicular standing surface acoustic waves allowing to position particles equidistant to each other on a grid. This experiment, called "acoustic tweezers", can be used for applications in material sciences, biology, physics, chemistry and nanotechnology.

Ultrasonic cleaning

Ultrasonic cleaners, sometimes mistakenly called *supersonic cleaners*, are used at frequencies from 20 to 40 kHz for jewellery, lenses and other optical parts, watches, dental instruments, surgical instruments, diving regulators and industrial parts. An ultrasonic cleaner works mostly by energy released from the collapse of millions of microscopic cavitations near the dirty surface. The bubbles made by cavitation collapse forming tiny jets directed at the surface.

Ultrasonic disintegration

Similar to ultrasonic cleaning, biological cells including bacteria can be disintegrated. High power ultrasound produces cavitation that facilitates particle disintegration or reactions. This has uses in biological science for analytical or chemical purposes (Sonication and Sonoporation) and in killing bacteria in sewage. Dr. Samir Khanal of Iowa State University employed high power ultrasound to disintegrate corn slurry to enhance liquefaction and saccharification for higher ethanol yield in dry corn milling plants.^[25] ^[26] Similar to these findings was Dr. Oleg Kozyuk able to improve ethanol yield with hydrodynamic cavitation.^[27] ^[28]

Ultrasonic humidifier

The ultrasonic humidifier, one type of nebulizer (a device that creates a very fine spray), is a popular type of humidifier. It works by vibrating a metal plate at ultrasonic frequencies to nebulize (sometimes incorrectly called "atomize") the water. Because the water is not heated for evaporation, it produces a cool mist. The ultrasonic pressure waves nebulize not only the water but also materials in the water including calcium, other minerals, viruses, fungi, bacteria,^[29] and other impurities. Illness caused by impurities that reside in a humidifier's reservoir fall under the heading of "Humidifier Fever".

Ultrasound Identification (USID)

Ultrasound Identification (USID) is a Real Time Locating System (RTLS) or Indoor Positioning System (IPS) technology used to automatically track and identify the location of objects in real time using simple, inexpensive nodes (badges/tags) attached to or embedded in objects and devices, which then transmit an ultrasound signal to communicate their location to microphone sensors.

Ultrasonic welding

In ultrasonic welding of plastics, high frequency (15 kHz to 40 kHz) low amplitude vibration is used to create heat by way of friction between the materials to be joined. The interface of the two parts is specially designed to concentrate the energy for the maximum weld strength.

Ultrasound and animals

Bats

Bats use a variety of ultrasonic ranging (echolocation) techniques to detect their prey. They can detect frequencies as high as 100 kHz, although there is some disagreement on the upper limit.^[30]

Rodents/insects

There is evidence that ultrasound in the range emitted by bats causes flying moths to make evasive manoeuvres because bats eat moths. Ultrasonic frequencies trigger a reflex action in the noctuid moth that cause it to drop a few inches in its flight to evade attack.^[31]

Tiger moths also emit clicks which jam bats' echolocation.^{[32] [33]}

Ultrasound generator/speaker systems are sold with claims that they frighten away rodents and insects, but there is no scientific evidence that the devices work.^{[34] [35] [36]}

Dogs

Dogs can hear sound at higher frequencies than humans can. A dog whistle exploits this by emitting a high frequency sound to call to a dog. Many dog whistles emit sound in the upper audible range of humans, but some, such as the **silent whistle**, emit ultrasound at a frequency in the range 18–22 kHz.

Dolphins and whales

It is well known that some whales can hear ultrasound and have their own natural sonar system. Some whales use the ultrasound as a hunting tool (for both detection of prey and as an attack).^[37]

Fish

Several types of fish can detect ultrasound. In the order Clupeiformes, members of the subfamily Alosinae (shad), have been shown to be able to detect sounds up to 180 kHz, while the other subfamilies (e.g. herrings) can hear only up to 4 kHz.^[38]

Horses

Diagnostic ultrasound is used externally in the equine for evaluation of soft tissue and tendon injuries, and internally in particular for reproductive work - evaluation of the reproductive tract of the mare and pregnancy detection^[39]. It may also be used in an external manner in stallions for evaluation of testicular condition and diameter as well as internally for reproductive evaluation (deferent duct etc.).^[40]



Bats use ultrasounds to move in the darkness.

Cattle

Starting at the turn of the century, ultrasound technology began to be used by the beef cattle industry to improve animal health and the yield of cattle operations.^[41] Ultrasound is used to evaluate fat thickness, rib eye area, and intramuscular fat in living animals.^[42] It is also used to evaluate the health and characteristics of unborn calves.

Ultrasound technology provides a means for cattle producers to obtain information that can be used to improve the breeding and husbandry of cattle. The technology can be expensive, and it requires a substantial time commitment for continuous data collection and operator training.^[42] Nevertheless, this technology has proven useful in managing and running a cattle breeding operation.^[41]

Sonochemistry

Power ultrasound in the 20–100 kHz range is used in chemistry. The ultrasound does not interact directly with molecules to induce the chemical change, as its typical wavelength (in the millimeter range) is too long compared to the molecules. Instead:

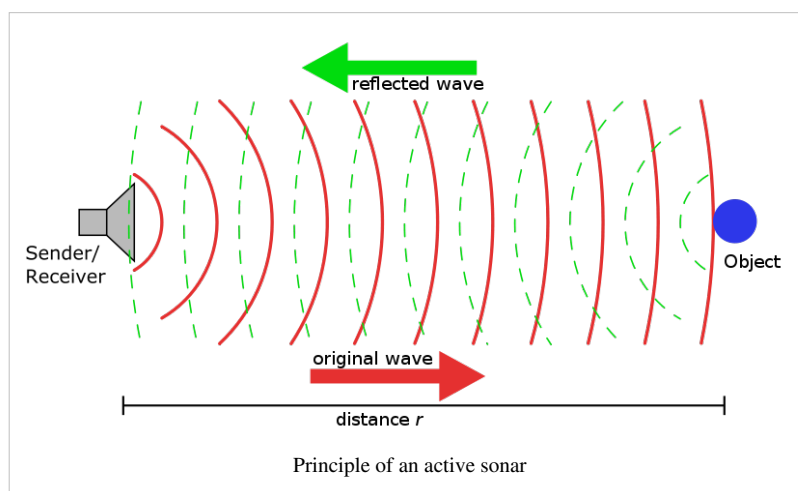
- It causes cavitation which causes local extremes of temperature and pressure in the liquid where the reaction happens.
- It breaks up solids and removes passivating layers of inert material to give a larger surface area for the reaction to occur over.

Both of these make the reaction faster. In 2008, Atul Kumar reported synthesis of Hantzsch esters and polyhydroquinoline derivatives via multi-component reaction protocol in aqueous micelles using ultrasound.^[43]

- It is used in extraction, using different frequencies.

Ultrasonic range finding

A common use of ultrasound is in range finding; this use is also called SONAR, (sound navigation and ranging). This works similarly to RADAR (radio detection and ranging): An ultrasonic pulse is generated in a particular direction. If there is an object in the path of this pulse, part or all of the pulse will be reflected back to the transmitter as an echo and can be detected through the receiver path. By measuring the difference in time between the pulse being transmitted and the echo being received, it is possible to determine how far away the object is.



The measured travel time of SONAR pulses in water is strongly dependent on the temperature and the salinity of the water. Ultrasonic ranging is also applied for measurement in air and for short distances. Such method is capable for easily and rapidly measuring the layout of rooms.

Although range finding underwater is performed at both sub-audible and audible frequencies for great distances (1 to several kilometers), ultrasonic range finding is used when distances are shorter and the accuracy of the distance measurement is desired to be finer. Ultrasonic measurements may be limited through barrier layers with large salinity, temperature or vortex differentials. Ranging in water varies from about hundreds to thousands of meters, but can be performed with centimeters to meters accuracy.

Other uses

Ultrasound when applied in specific configurations can produce short bursts of light in an exotic phenomenon known as sonoluminescence. This phenomenon is being investigated partly because of the possibility of bubble fusion (a nuclear fusion reaction hypothesized to occur during sonoluminescence).

Researchers have successfully used ultrasound to regenerate dental material^[44].

Ultrasound is used when characterizing particulates through the technique of ultrasound attenuation spectroscopy or by observing electroacoustic phenomena.

In rheology, an acoustic rheometer relies on the principle of ultrasound. In fluid mechanics, fluid flow can be measured using an ultrasound flow meter.

Ultrasound also plays a role in Sonic weaponry.

High and ultra high ultrasound waves are used in Acoustic microscopy

Audio can be propagated by modulated ultrasound.

Nonlinear propagation effects

Because of their high amplitude to wavelength ratio, ultrasonic waves commonly display nonlinear propagation.

Safety

Occupational exposure to ultrasound in excess of 120 dB may lead to hearing loss. Exposure in excess of 155 dB may produce heating effects that are harmful to the human body, and it has been calculated that exposures above 180 dB may lead to death.^[45]

See also

- Acoustics
 - Bat detector
 - Infrasound — sound at extremely low frequencies
 - Light
 - Medical ultrasonography
 - Picosecond Ultrasonics
 - Sound
 - Sound from ultrasound (also known as Hypersonic sound)
 - Waves
 - Sonomicrometry
 - Zone sonography technology
-

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Further reading

- Kundu, Tribikram. *Ultrasonic nondestructive evaluation: engineering and biological material characterization*. Boca Raton, FL: CRC Press, c2004. ISBN 0-8493-1462-3.

External links

- Guidelines for the Safe Use of Ultrasound (http://www.hc-sc.gc.ca/ewh-semt/pubs/radiation/safety-code_24-securite/health-sante-eng.php): valuable insight on the boundary conditions tending towards abuse of ultrasound.
- High-frequency hearing risk for operators of industrial ultrasonic devices (<http://www.ncbi.nlm.nih.gov/pubmed/6654504>):
- Safety Issues in Fetal Ultrasound (<http://www.fetalultrasoundsafety.net/Downloads/fetalultrasoundsafety.pdf>):
- Damage to red blood cells induced by acoustic cavitation(ultrasound) (<http://cat.inist.fr/?aModele=afficheN&cpsidt=3419382>):

Medical ultrasonography

Diagnostic sonography (ultrasonography) is an ultrasound-based diagnostic imaging technique used to visualize subcutaneous body structures including tendons, muscles, joints, vessels and internal organs for possible pathology or lesions. Obstetric sonography is commonly used during pregnancy and is widely recognized by the public.

In physics, the term "ultrasound" applies to all acoustic energy (longitudinal, mechanical wave) with a frequency above the audible range of human hearing. The audible range of sound is 20 hertz-20 kilohertz. Ultrasound is frequency greater than 20 kilohertz.

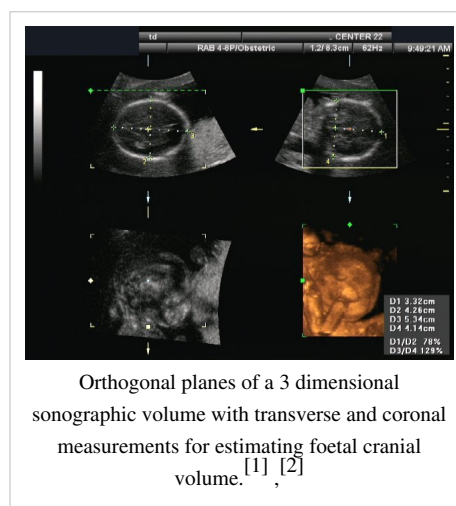
Diagnostic applications

Typical diagnostic sonographic scanners operate in the frequency range of 2 to 18 megahertz, though frequencies up to 50-100 megahertz has been used experimentally in a technique known as biomicroscopy in special regions, such as the anterior chamber of eye. The above frequencies are hundreds of times greater than the limit of human hearing, which is typically accepted as 20 kilohertz. The choice of frequency is a trade-off between spatial resolution of the image and imaging depth: lower frequencies produce less resolution but image deeper into the body.

Sonography (ultrasonography) is widely used in medicine. It is possible to perform both diagnosis and therapeutic procedures, using ultrasound to guide interventional procedures (for instance biopsies or drainage of fluid collections). Sonographers are medical professionals who perform scans for diagnostic purposes. Sonographers typically use a hand-held probe (called a transducer) that is placed directly on and moved over the patient.

Sonography is effective for imaging soft tissues of the body. Superficial structures such as muscles, tendons, testes, breast and the neonatal brain are imaged at a higher frequency (7-18 MHz), which provides better axial and lateral resolution. Deeper structures such as liver and kidney are imaged at a lower frequency 1-6 MHz with lower axial and lateral resolution but greater penetration.

Medical sonography is used in the study of many different systems:



System	Description	See also
Cardiology	Echocardiography is an essential tool in cardiology, to diagnose e.g. dilatation of parts of the heart and function of heart ventricles and valves	see echocardiography
Emergency Medicine	Point of care ultrasound has many applications in the Emergency Department, including the Focused Assessment with Sonography for Trauma (FAST) exam for assessing significant hemoperitoneum or pericardial tamponade after trauma. Ultrasound is routinely used in the Emergency Department to expedite the care of patients with right upper quadrant abdominal pain who may have gallstones or cholecystitis.	see FAST exam
Gastroenterology	In abdominal sonography, the solid organs of the abdomen such as the pancreas, aorta, inferior vena cava, liver, gall bladder, bile ducts, kidneys, and spleen are imaged. Sound waves are blocked by gas in the bowel and attenuated in different degree by fat, therefore there are limited diagnostic capabilities in this area. The appendix can sometimes be seen when inflamed e.g.: appendicitis.	
Gynecology		see gynecologic ultrasonography

Neurology	for assessing blood flow and stenoses in the carotid arteries (Carotid ultrasonography) and the big intracerebral arteries	see Carotid ultrasonography. Intracerebral: see Transcranial Doppler
Obstetrics	Obstetrical ultrasound is commonly used during pregnancy to check on the development of the fetus.	see obstetric ultrasonography
Ophthalmology		see A-scan ultrasonography, B-scan ultrasonography
Urology	to determine, for example, the amount of fluid retained in a patient's bladder. In a pelvic sonogram, organs of the pelvic region are imaged. This includes the uterus and ovaries or urinary bladder. Men are sometimes given a pelvic sonogram to check on the health of their bladder and prostate. There are two methods of performing a pelvic sonography - externally or internally. The internal pelvic sonogram is performed either transvaginally (in a woman) or transrectally (in a man). Sonographic imaging of the pelvic floor can produce important diagnostic information regarding the precise relationship of abnormal structures with other pelvic organs and it represents a useful hint to treat patients with symptoms related to pelvic prolapse, double incontinence and obstructed defecation. ^[3]	
Musculoskeletal	tendons, muscles, nerves, ligaments, soft tissue masses, and bone surfaces	
Cardiovascular system	To assess patency and possible obstruction of arteries Arterial sonography, diagnose DVT (Thrombosonography) and determine extent and severity of venous insufficiency (venosonography)	Intravascular ultrasound

Other types of uses include:

- Interventional; biopsy, emptying fluids, intrauterine transfusion (Hemolytic disease of the newborn)
- Contrast-enhanced ultrasound

A general-purpose sonographic machine may be used for most imaging purposes. Usually specialty applications may be served only by use of a specialty transducer. Most ultrasound procedures are done using a transducer on the surface of the body, but improved diagnostic confidence is often possible if a transducer can be placed inside the body. For this purpose, specialty transducers, including endovaginal, endorectal, and transesophageal transducers are commonly employed. At the extreme of this, very small transducers can be mounted on small diameter catheters and placed into blood vessels to image the walls and disease of those vessels.

Therapeutic applications

Therapeutic applications use ultrasound to bring heat or agitation into the body. Therefore much higher energies are used than in diagnostic ultrasound. In many cases the range of frequencies used are also very different.

- Ultrasound is sometimes used to clean teeth in dental hygiene.
- Ultrasound sources may be used to generate regional heating and mechanical changes in biological tissue, e.g. in occupational therapy, physical therapy and cancer treatment. However the use of ultrasound in the treatment of musculoskeletal conditions has fallen out of favor.^{[4] [5]}
- Focused ultrasound may be used to generate highly localized heating to treat cysts and tumors (benign or malignant), This is known as Focused Ultrasound Surgery (FUS) or High Intensity Focused Ultrasound (HIFU). These procedures generally use lower frequencies than medical diagnostic ultrasound (from 250 kHz to 2000 kHz), but significantly higher energies. HIFU treatment is often guided by MRI.
- Focused ultrasound may be used to break up kidney stones by lithotripsy.
- Ultrasound may be used for cataract treatment by phacoemulsification.
- Additional physiological effects of low-intensity ultrasound have recently been discovered, e.g. its ability to stimulate bone-growth and its potential to disrupt the blood-brain barrier for drug delivery.
- Procoagulant at 5-12 MHz,

From sound to image

The creation of an image from sound is done in three steps - producing a sound wave, receiving echoes, and interpreting those echoes.

Producing a sound wave

A sound wave is typically produced by a piezoelectric transducer encased in a housing which can take a number of forms. Strong, short electrical pulses from the ultrasound machine make the transducer ring at the desired frequency. The frequencies can be anywhere between 2 and 18 MHz. The sound is focused either by the shape of the transducer, a lens in front of the transducer, or a complex set of control pulses from the ultrasound scanner machine (Beamforming). This focusing produces an arc-shaped sound wave from the face of the transducer. The wave travels into the body and comes into focus at a desired depth.

Older technology transducers focus their beam with physical lenses. Newer technology transducers use phased array techniques to enable the sonographic machine to change the direction and depth of focus. Almost all piezoelectric transducers are made of ceramic.

Materials on the face of the transducer enable the sound to be transmitted efficiently into the body (usually seeming to be a rubbery coating, a form of impedance matching). In addition, a water-based gel is placed between the patient's skin and the probe.

The sound wave is partially reflected from the layers between different tissues. Specifically, sound is reflected anywhere there are density changes in the body: e.g. blood cells in blood plasma, small structures in organs, etc. Some of the reflections return to the transducer.

Receiving the echoes

The return of the sound wave to the transducer results in the same process that it took to send the sound wave, except in reverse. The return sound wave vibrates the transducer, the transducer turns the vibrations into electrical pulses that travel to the ultrasonic scanner where they are processed and transformed into a digital image.

Forming the image

The sonographic scanner must determine three things from each received echo:

1. How long it took the echo to be received from when the sound was transmitted.
2. From this the focal length for the phased array is deduced, enabling a sharp image of that echo at that depth (this is not possible while producing a sound wave).
3. How strong the echo was. It could be noted that sound wave is not a click, but a pulse with a specific carrier frequency. Moving objects change this frequency on reflection, so that it is only a matter of electronics to have simultaneous Doppler sonography.

Once the ultrasonic scanner determines these three things, it can locate which pixel in the image to light up and to what intensity and at what hue if frequency is processed (see redshift for a natural mapping to hue).

Transforming the received signal into a digital image may be explained by using a blank spreadsheet as an analogy. First picture a long, flat transducer at the top of the sheet. Send pulses down the 'columns' of the spreadsheet (A, B,



Medical sonographic instrument

C, etc.). Listen at each column for any return echoes. When an echo is heard, note how long it took for the echo to return. The longer the wait, the deeper the row (1,2,3, etc.). The strength of the echo determines the brightness setting for that cell (white for a strong echo, black for a weak echo, and varying shades of grey for everything in between.) When all the echoes are recorded on the sheet, we have a greyscale image.

Displaying the image

Images from the sonographic scanner can be displayed, captured, and broadcast through a computer using a frame grabber to capture and digitize the analog video signal. The captured signal can then be post-processed on the computer itself.^[6]

For computational details see also: Confocal laser scanning microscopy, Radar,

Sound in the body

Ultrasonography (sonography) uses a probe containing one or more acoustic transducers to send pulses of sound into a material. Whenever a sound wave encounters a material with a different density (acoustical impedance), part of the sound wave is reflected back to the probe and is detected as an echo. The time it takes for the echo to travel back to the probe is measured and used to calculate the depth of the tissue interface causing the echo. The greater the difference between acoustic impedances, the larger the echo is. If the pulse hits gases or solids, the density difference is so great that most of the acoustic energy is reflected and it becomes impossible to see deeper.



The frequencies used for medical imaging are generally in the range of 1 to 18 MHz. Higher frequencies have a correspondingly smaller wavelength, and can be used to make sonograms with smaller details. However, the attenuation of the sound wave is increased at higher frequencies, so in order to have better penetration of deeper tissues, a lower frequency (3-5 MHz) is used.

Seeing deep into the body with sonography is very difficult. Some acoustic energy is lost every time an echo is formed, but most of it (approximately $0.3 \frac{\text{dB}}{\text{cm depth} \cdot \text{MHz}}$) is lost from acoustic absorption.

The speed of sound varies as it travels through different materials, and is dependent on the acoustical impedance of the material. However, the sonographic instrument assumes that the acoustic velocity is constant at 1540 m/s. An effect of this assumption is that in a real body with non-uniform tissues, the beam becomes somewhat de-focused and image resolution is reduced.

To generate a 2D-image, the ultrasonic beam is swept. A transducer may be swept mechanically by rotating or swinging. Or a 1D phased array transducer may be used to sweep the beam electronically. The received data is processed and used to construct the image. The image is then a 2D representation of the slice into the body.

3D images can be generated by acquiring a series of adjacent 2D images. Commonly a specialised probe that mechanically scans a conventional 2D-image transducer is used. However, since the mechanical scanning is slow, it is difficult to make 3D images of moving tissues. Recently, 2D phased array transducers that can sweep the beam in 3D have been developed. These can image faster and can even be used to make live 3D images of a beating heart.

Doppler ultrasonography is used to study blood flow and muscle motion. The different detected speeds are represented in color for ease of interpretation, for example leaky heart valves: the leak shows up as a flash of unique color. Colors may alternatively be used to represent the amplitudes of the received echoes.

Modes of sonography

Several different modes of ultrasound are used in medical imaging.^[7] These are:

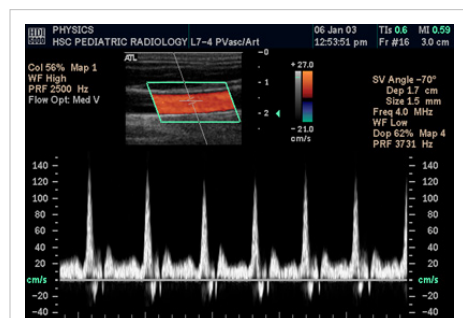
- **A-mode:** A-mode is the simplest type of ultrasound. A single transducer scans a line through the body with the echoes plotted on screen as a function of depth. Therapeutic ultrasound aimed at a specific tumor or calculus is also A-mode, to allow for pinpoint accurate focus of the destructive wave energy.
- **B-mode:** In B-mode ultrasound, a linear array of transducers simultaneously scans a plane through the body that can be viewed as a two-dimensional image on screen.
- **M-mode:** M stands for motion. In m-mode a rapid sequence of B-mode scans whose images follow each other in sequence on screen enables doctors to see and measure range of motion, as the organ boundaries that produce reflections move relative to the probe.
- **Doppler mode:** This mode makes use of the Doppler effect in measuring and visualizing blood flow
 - **Color doppler:** Velocity information is presented as a color coded overlay on top of a B-mode image
 - **Continuous doppler:** Doppler information is sampled along a line through the body, and all velocities detected at each time point is presented (on a time line)
 - **Pulsed wave (PW) doppler:** Doppler information is sampled from only a small sample volume (defined in 2D image), and presented on a timeline
 - **Duplex:** a common name for the simultaneous presentation of 2D and (usually) PW doppler information. (Using modern ultrasound machines color doppler is almost always also used, hence the alternative name **Triplex**.)

Midwives generally use this type of system.

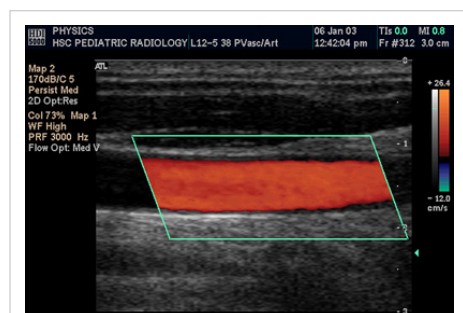
Doppler sonography

Sonography can be enhanced with Doppler measurements, which employ the Doppler effect to assess whether structures (usually blood) are moving towards or away from the probe, and its relative velocity. By calculating the frequency shift of a particular sample volume, for example flow in an artery or a jet of blood flow over a heart valve, its speed and direction can be determined and visualised. This is particularly useful in cardiovascular studies (sonography of the vascular system and heart) and essential in many areas such as determining reverse blood flow in the liver vasculature in portal hypertension. The Doppler information is displayed graphically using spectral Doppler, or as an image using color Doppler (directional Doppler) or power Doppler (non directional Doppler). This Doppler shift falls in the audible range and is often presented audibly using stereo speakers: this produces a very distinctive, although synthetic, pulsating sound.

Most modern sonographic machines use pulsed Doppler to measure velocity. Pulsed wave machines transmit and receive series of pulses. The frequency shift of each pulse is ignored, however the relative phase changes of the pulses are used to obtain the frequency shift (since frequency is the rate of change of phase). The major advantages of pulsed Doppler over continuous wave is



Spectral Doppler of Common Carotid Artery



Colour Doppler of Common Carotid Artery

that distance information is

obtained (the time between the transmitted and received pulses can be converted into a distance with knowledge of the speed of sound) and gain correction is applied. The disadvantage of pulsed Doppler is that the measurements can suffer from aliasing. The terminology "Doppler ultrasound" or "Doppler sonography", has been accepted to apply to both pulsed and continuous Doppler systems despite the different mechanisms by which the velocity is measured.

It should be noted here that there are no standards for the display of color Doppler. Some laboratories insist on showing arteries as red and veins as blue, as medical illustrators usually show them, even though, as a result, a tortuous vessel may have portions with flow toward and away relative to the transducer. This can result in the illogical appearance of blood flow that appears to be in both directions in the same vessel. Other laboratories use red to indicate flow toward the transducer and blue away from the transducer which is the reverse of 150 years of astronomical literature on the Doppler effect. Still other laboratories prefer to display the sonographic Doppler color map more in accord with the prior published physics with the red shift representing longer waves of echoes (scattered) from blood flowing away from the transducer; and with blue representing the shorter waves of echoes reflecting from blood flowing toward the transducer. Because of this confusion and lack of standards in the various laboratories, the sonographer must understand the underlying acoustic physics of color Doppler and the physiology of normal and abnormal blood flow in the human body.^{[8] [9] [10] [11]}



Computer-enhanced transcranial doppler.

Contrast media

The use of microbubble contrast media in medical sonography to improve ultrasound signal backscatter is known as contrast-enhanced ultrasound. This technique is currently used in echocardiography, and may have future applications in molecular imaging and drug delivery.

Compression ultrasonography

Compression ultrasonography is a technique used for diagnosing deep vein thrombosis and combines ultrasonography of the deep veins with venous compression.^[12] The technique can be used on deep veins of the upper and lower extremities, with some laboratories limiting the examination to the common femoral vein and the popliteal vein, whereas other laboratories examine the deep veins from the inguinal region to the calf, including the calf veins.^[12]

Compression ultrasonography in B-mode has both high sensitivity and specificity for detecting proximal deep vein thrombosis in symptomatic patients. The sensitivity lies somewhere between 90 to 100% for the diagnosis of symptomatic deep vein thrombosis, and the specificity ranges between 95 to 100%.^[12]

Attributes

As with all imaging modalities, ultrasonography has its list of positive and negative attributes.

Strengths

- It images muscle, soft tissue, and bone surfaces very well and is particularly useful for delineating the interfaces between solid and fluid-filled spaces.
- It renders "live" images, where the operator can dynamically select the most useful section for diagnosing and documenting changes, often enabling rapid diagnoses. Live images also allow for ultrasound-guided biopsies or injections, which can be cumbersome with other imaging modalities.
- It shows the structure of organs.
- It has no known long-term side effects and rarely causes any discomfort to the patient.
- Equipment is widely available and comparatively flexible.
- Small, easily carried scanners are available; examinations can be performed at the bedside.
- Relatively inexpensive compared to other modes of investigation, such as computed X-ray tomography, DEXA or magnetic resonance imaging.
- Spatial resolution is better in high frequency ultrasound transducers than it is in most other imaging modalities.
- Through the use of an Ultrasound research interface, an ultrasound device can offer a relatively inexpensive, real-time, and flexible method for capturing data required for special research purposes for tissue characterization and development of new image processing techniques

Weaknesses

- Sonographic devices have trouble penetrating bone. For example, sonography of the adult brain is very limited though improvements are being made in transcranial ultrasonography.
- Sonography performs very poorly when there is a gas between the transducer and the organ of interest, due to the extreme differences in acoustic impedance. For example, overlying gas in the gastrointestinal tract often makes ultrasound scanning of the pancreas difficult, and lung imaging is not possible (apart from demarcating pleural effusions).
- Even in the absence of bone or air, the depth penetration of ultrasound may be limited depending on the frequency of imaging. Consequently, there might be difficulties imaging structures deep in the body, especially in obese patients.
- Body habitus has a large influence on image quality, image quality and accuracy of diagnosis is limited with obese patients, overlying subcutaneous fat attenuates the sound beam and a lower frequency transducer is required (with lower resolution)

The method is operator-dependent. A high level of skill and experience is needed to acquire good-quality images and make accurate diagnoses.

- There is no scout image as there is with CT and MRI. Once an image has been acquired there is no exact way to tell which part of the body was imaged.

Risks and side-effects

Ultrasonography is generally considered a "safe" imaging modality.^[13] However slight detrimental effects have been occasionally observed (see below). Diagnostic ultrasound studies of the foetus are generally considered to be safe during pregnancy. This diagnostic procedure should be performed only when there is a valid medical indication, and the lowest possible ultrasonic exposure setting should be used to gain the necessary diagnostic information under the "as low as reasonably achievable" or ALARA principle.

World Health Organizations technical report series 875(1998).^[14] supports that ultrasound is harmless: "Diagnostic ultrasound is recognized as a safe, effective, and highly flexible imaging modality capable of providing clinically relevant information about most parts of the body in a rapid and cost-effective fashion". Although there is no evidence ultrasound could be harmful for the foetus, US Food and Drug Administration views promotion, selling, or leasing of ultrasound equipment for making "keepsake foetal videos" to be an unapproved use of a medical device.

Studies on the safety of ultrasound

- A study at the Yale School of Medicine found a correlation between prolonged and frequent use of ultrasound and abnormal neuronal migration in mice.^[15] A meta-analysis of several ultrasonography studies found no statistically significant harmful effects from ultrasonography, but mentioned that there was a lack of data on long-term substantive outcomes such as neurodevelopment.^[16]

Regulation

Diagnostic and therapeutic ultrasound equipment is regulated in the USA by the FDA, and worldwide by other national regulatory agencies. The FDA limits acoustic output using several metrics. Generally other regulatory agencies around the world accept the FDA-established guidelines.

Currently New Mexico is the only state in the USA which regulates diagnostic medical sonographers. Certification examinations for sonographers are available in the US from three organizations: The American Registry of Diagnostic Medical Sonography^[17], Cardiovascular Credentialing International^[18] and the American Registry of Radiological Technologists^[19].

The primary regulated metrics are MI (Mechanical Index) a metric associated with the cavitation bio-effect, and TI (Thermal Index) a metric associated with the tissue heating bio-effect. The FDA requires that the machine not exceed limits that they have established. This requires self-regulation on the part of the manufacturer in terms of the calibration of the machine. The established limits are reasonably conservative so as to maintain diagnostic ultrasound as a safe imaging modality.^[20]

In India, lack of social security and consequent preference for a male child has popularized the use of ultrasound technology to identify and abort female foetuses. India's Pre-natal Diagnostic Techniques act makes use of ultrasound for sex selection illegal,^[21] but unscrupulous Indian doctors and would-be parents continue to discriminate against the girl child.

Career Information

According to the Society of Diagnostic Medical Sonography^[22], a diagnostic medical sonographer in the United States of America earns an average of \$66,768 (2008). Sonographers work in a variety of settings including hospitals, clinics, physician offices, and mobile labs. Some even use their skills and knowledge in veterinary offices. Information^[23] about a career in Diagnostic Medical Sonography is available from the Society of Diagnostic Medical Sonography. The US Department of Labor also provides information about the field in its Occupation Outlook Handbook^[24].

History

United States

Ultrasonic energy was first applied to the human body for medical purposes by Dr. George Ludwig at the Naval Medical Research Institute, Bethesda, Maryland in the late 1940s.^[25] ^[26] English born and educated John Wild (1914–2009) first used ultrasound to assess the thickness of bowel tissue as early as 1949: for his early work he has been described as the "father of medical ultrasound".^[27]

In 1962, after about two years of work, Joseph Holmes, William Wright, and Ralph Meyerdirk developed the first compound contact B-mode scanner. Their work had been supported by U.S. Public Health Services and the University of Colorado. Wright and Meyerdirk left the University to form Physionic Engineering Inc., which launched the first commercial hand-held articulated arm compound contact B-mode scanner in 1963. This was the start of the most popular design in the history of ultrasound scanners.^[28]

The first demonstration of color Doppler was by Geoff Stevenson, who was involved in the early developments and medical use of Doppler shifted ultrasonic energy.^[29]

Sweden

Medical ultrasonography was used 1953 at Lund University by cardiologist Inge Edler and Carl Hellmuth Hertz, the son of Gustav Ludwig Hertz, who was a graduate student at the department of nuclear physics.

Edler had asked Hertz if it was possible to use radar to look into the body, but Hertz said this was impossible. However, he said, it might be possible to use ultrasonography. Hertz was familiar with using ultrasonic reflectoscopes for nondestructive materials testing, and together they developed the idea of using this method in medicine.

The first successful measurement of heart activity was made on October 29, 1953 using a device borrowed from the ship construction company Kockums in Malmö. On December 16 the same year, the method was used to generate an echo-encephalogram (ultrasonic probe of the brain). Edler and Hertz published their findings in 1954.^[30]

Scotland

Parallel developments in Glasgow, Scotland by Professor Ian Donald and colleagues at the Glasgow Royal Maternity Hospital (GRMH) led to the first diagnostic applications of the technique. Donald was an obstetrician with a self-confessed "childish interest in machines, electronic and otherwise", who, having treated the wife of one of the company's directors, was invited to visit the Research Department of boilermakers Babcock & Wilcox at Renfrew, where he used their industrial ultrasound equipment to conduct experiments on various morbid anatomical specimens and assess their ultrasonic characteristics. Together with the medical physicist Tom Brown and fellow obstetrician Dr John MacVicar, Donald refined the equipment to enable differentiation of pathology in live volunteer patients. These findings were reported in *The Lancet* on 7 June 1958^[31] as "Investigation of Abdominal Masses by Pulsed Ultrasound" - possibly one of the most important papers ever published in the field of diagnostic medical imaging.

At GRMH, Professor Donald and Dr James Willocks then refined their techniques to obstetric applications including foetal head measurement to assess the size and growth of the foetus. With the opening of the new Queen Mother's Hospital in Yorkhill in 1964, it became possible to improve these methods even further. Dr Stuart Campbell's pioneering work on foetal cephalometry led to it acquiring long-term status as the definitive method of study of foetal growth. As the technical quality of the scans was further developed, it soon became possible to study pregnancy from start to finish and diagnose its many complications such as multiple pregnancy, foetal abnormality and *placenta praevia*. Diagnostic ultrasound has since been imported into practically every other area of medicine.

See also

- Emergency ultrasound
- 3D ultrasound
- Duplex ultrasonography
- Doppler fetal monitor
- European Master in Molecular Imaging

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External links

- American Institute of Ultrasound in Medicine (<http://www.aium.org>) Professional Association
 - About the discovery of medical ultrasonography (<http://www.ob-ultrasound.net/ingehertz.html>)
 - History of medical sonography (ultrasound) (<http://www.ob-ultrasound.net/history1.html>)
 - Procedures in Ultrasound (Sonography) (<http://radiologyinfo.org/en/sitemap/modal-alias.cfm?modal=US>) for patients, from RadiologyInfo.org
 - Careers in the vascular ultrasound field (<http://www.svunet.org/i4a/pages/index.cfm?pageid=3322>)
 - Sonography of the female pelvic floor:clinical indications and techniques (http://www.pelviperineology.org/practical/sonography_female_pelvic_floor_clinical_indications_and_techniques.html) Illustrate the clinical utility of this non-invasive diagnostic technique.
 - How to Become an Ultrasound Technician - a wiki article on becoming an ultrasound technician.
 - A Pilot Study of Comprehensive Ultrasound Education at the Wayne State University School of Medicine: <http://www.jultrasoundmed.org/cgi/content/abstract/27/5/745?ck=nck>
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Advanced Experimental Techniques and Methods

Optical Tomography and Imaging

Optical imaging is an imaging technique.

Optics usually describes the behavior of visible, ultraviolet, and infrared light used in imaging.

Because light is an electromagnetic wave, similar phenomena occur in X-rays, microwaves, radio waves. Chemical imaging or molecular imaging ^[1] ^[2] ^[3] involves inference from the deflection of light emitted from (e.g. laser, infrared) source to structure, texture, anatomic and chemical properties of material (e.g. crystal, cell tissue). Optical imaging systems may be divided into diffusive ^[4] and ballistic imaging ^[5] systems.

Diffusive optical imaging in neuroscience

Diffusive optical imaging (also known as *Near Infrared Optical Tomography* or NIROT) is a technique that gives neuroscientists the ability to simultaneously obtain information about the source of neural activity as well as its time course. In other words, it allows them to "see" neural activity and study the functioning of the brain.

In this method, a near-infrared laser is positioned on the scalp. Detectors composed of optical fiber bundles are located a few centimeters away from the light source. These detectors sense how the path of light is altered, either through absorption or scattering, as it traverses brain tissue.

This method can provide two types of information. First, it can be used to measure the absorption of light, which is related to concentration of chemicals in the brain. Second, it can measure the scattering of light, which is related to physiological characteristics such as the swelling of glia and neurons that are associated with neuronal firing.

Typical applications include rapid 2D optical *topographic* imaging of the event-related optical signal (EROS) or Near infrared spectroscopy (NIRS) signal following brain activity and *tomographic* reconstruction of an entire 3D volume of tissue to diagnose breast cancer or neonatal brain haemorrhage. The spatial resolution of DOT techniques is several millimeters, comparable to the lower end of functional magnetic resonance imaging (fMRI). The temporal resolution of EROS is very good, comparable to electroencephalography, and magnetoencephalography (~milliseconds), while that of NIRS, which measures hemodynamic changes rather than neuronal activity, is comparable to fMRI (~seconds). DOT instruments are relatively low cost (\$150,000), portable and immune to electrical interference. The signal-to-noise ratio of NIRS is quite good, enabling detection of responses to single events in many cases. EROS signals are much weaker, typically requiring averaging of many responses.

Important chemicals that this method can detect include hemoglobin and cytochromes.

Ballistic optical imaging

Ballistic optical imaging systems ignore the diffused photons and rely only on the ballistic photons to create high-resolution (near diffraction limited) images through scattering media.

See also

- Photon diffusion
- Ballistic imaging
- Photon diffusion equation

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External links

- Understanding Near-Infrared Imaging (http://www.licor.com/bio/products/imaging_systems/pearl/pearl_sensitivity.jsp/) – Resource to better understand the benefits of Near-Infrared imaging.
- Diffuse Optics Lab at University of Pennsylvania, Philadelphia (<http://www.lrsn.upenn.edu/pmi>)
- DOI at Massachusetts General Hospital, Boston (<http://www.nmr.mgh.harvard.edu/martinos/research/technologiesDOI.php>)
- Biomedical Imaging Group at Dartmouth (<http://www-nml.dartmouth.edu/biomedprg/biomed.html>)
- DOS/I Lab at the Beckman Laser Institute, University of California, Irvine (<http://dosi.bli.uci.edu>)
- A review article in the field by A.P. Gibson et al. (<http://www.iop.org/EJ/abstract/0031-9155/50/4/R01>)
- An article on optical breast imaging (<http://medicalphysicsweb.org/cws/article/research/27299>)
- Illinois ECE 460 Principles of Optical Imaging (<http://nanohub.org/resources/5163>) Course lecture notes

Breast cancer screening

Breast cancer screening refers to testing otherwise-healthy women for breast cancer in an attempt to achieve an earlier diagnosis. The assumption is that early detection will improve outcomes. A number of screening test have been employed including: clinical and self breast exams, mammography, genetic screening, ultrasound, and magnetic resonance imaging.

A clinical or self breast exam involves feeling the breast for lumps or other abnormalities. Evidence however does not support its use.^[1] Mammographic screening for breast cancer is also controversial. The Cochrane collaboration in 2009 concluded that it is unclear whether screening does more good than harm.^[2] Many national organizations still however recommend it. If mammography is decided up it should only be done every two years in women between the ages of 50 and 74.^[3] Several tools are available to help target breast cancer screening to older women with longer life expectancies.^[4]

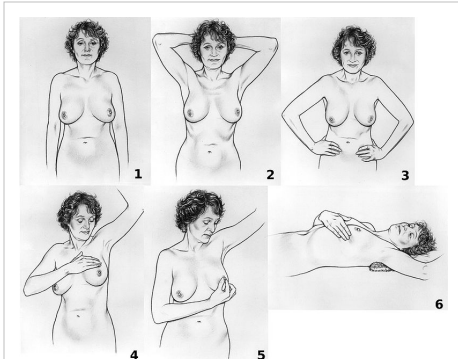
Abnormal findings on screening are further investigated by surgically removing a piece of the suspicious lumps (biopsy) to examine them under the microscope. Ultrasound may be used to guide the biopsy needle during the procedure. Magnetic resonance imaging is used to guide treatment, but is not an established screening method for healthy women.

Women with a family history of breast and ovarian cancer have a higher risk of mutations of the BRCA1 and BRCA2 genes. These mutations result in a higher risk of breast cancer. Testing for these genes is expensive and not done routinely. However those with this mutation should be screened more aggressively: starting at an earlier age, with greater frequency, and possibly with magnetic resonance imaging.

Breast exam

Breast examination (either clinical breast exams (CBE) by a health care provider or by self exams) were once widely recommended. They however are not supported by evidence and may contribute to harm. Their use in women without symptoms and at low risk is thus controversial.^[5]

A 2003 Cochrane review found no benefit in terms of mortality from screening by breast self-examination or by clinical exam, but rather that they do possible harm in terms of increased numbers of benign lesions identified and an increased number of biopsies performed. They conclude "screening by breast self-examination or physical examination cannot be recommended." ^[1]



An pictorial example of breast self-examination in six steps. Steps 1-3 involve inspection of the breast with the arms hanging next to the body, behind the head and in the side. Step 4 is palpation of the breast. Step 5 is palpation of the nipple. Step 6 is palpation of the breast while lying down.

Mammography

Mammography is a common screening method, since it is relatively fast and widely available in developed countries. When detected by mammography breast cancers are usually smaller (in an earlier stage) than those detected by patients or doctors as a breast lump, and presumably treatment in an earlier stage will improve outcome. This assertion however has been challenged by recent reviews which have found the significance of these benefits to be questionable.

A 2009 Cochrane review estimated that mammography in women between 50 and 75 years old results in a relative risk reduction of death from breast cancer of 15% or an absolute risk reduction of 0.05%. Those who have mammograms however end up with increased surgeries, chemotherapy, radiotherapy and other potentially procedures resulting from the over-detection of harmless lumps.^[2] Consequently, the value of routine mammography in women at low or average risk is controversial.^[2] With unnecessary treatment of ten women for every one woman whose life was prolonged, the authors concluded that routine mammography may do more harm than good.^[2]

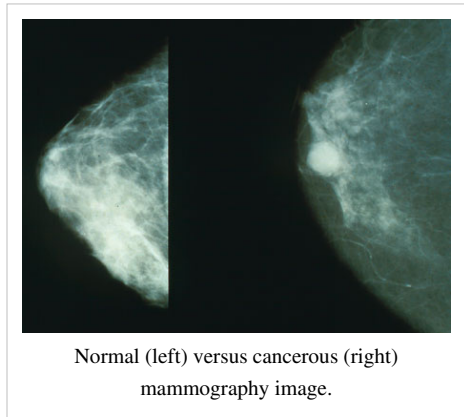
A 2009 U.S. Preventive Services Task Force analysis come to similar conclusions: for women in their 40s 2000 would need to be screened for 10 years, resulting in 1000 people with false results and 250 unnecessary biopsies to prevent 1 breast cancer death, for women in their 50s 1339 would need to be screened for 10 years to prevent a single breast cancer related death, and for women in their 60s 377 women would need to be screened for 10 years.^[6]

An analysis of Norwegians published in 2010 found a 10% reduction in breast cancer mortality (2.4 deaths per 100,000 person-years) attributable to screening but this difference was non significant.^[7]

For places that recommend screening the age at which this should begin and how frequently women differ around the world. In the UK, all women are invited for screening once every three years beginning at age 50. As of 2009 the US Preventive Services Task Force recommends that women over the age of 50 receive mammography once every two years.^[8]

Women at higher risk may benefit from earlier or more frequent screening. Women with one or more first-degree relatives (mother, sister, daughter) with premenopausal breast cancer often begin screening at an earlier age, perhaps at an age 10 years younger than the age when the relative was diagnosed with breast cancer.

Mammography is not generally considered as an effective screening technique for women less than 50 years old. A systematic review by the American College of Physicians concluded that, for women 40 to 49 years of age, the risks of mammography outweighed the benefits,^[9] and the US Preventive Services Task Force says that the evidence in favor of routine screening of women under the age of 50 is "weak".^[8] Part of the difficulty in interpreting mammograms in younger women stems from breast density. Radiographically, a dense breast has a preponderance of glandular tissue, and younger age or estrogen hormone replacement therapy contribute to mammographic breast density. After menopause, the breast glandular tissue gradually is replaced by fatty tissue, making mammographic interpretation much more accurate. Some authors speculate that part of the contribution of estrogen Hormone replacement therapy to breast cancer mortality arises from the issue of increased mammographic breast density.



Enhancements

In general, digital mammography and computer-aided mammography have increased the sensitivity of mammograms, but this may come at the cost of more numerous false positive results..

Computer-aided diagnosis(CAD) Systems may help radiologists to evaluate X-ray images to detect breast cancer in an early stage. CAD is especially established in US and the Netherlands. It is used in addition to the human evaluation of the diagnostician.

Health programs

In 2005, 67.9% of all U.S. women age 40–64 had a mammogram in the past two years (74.5% of women with private health insurance, 56.1% of women with Medicaid insurance, 38.1% of currently uninsured women, and 32.9% of women uninsured for > 12 months).^[10] All U.S. states (except Utah) mandate that private health insurance plans and Medicaid provide some coverage for breast cancer screening.^[11] Section 4101 of the Balanced Budget Act of 1997 required that Medicare (available to those aged 65 or older or who have been on Social Security Disability Insurance for over 2 years), effective January 1, 1998, cover and waive the Part B deductible for annual screening mammography in women aged 40 or older.

All organized breast cancer screening programs in Canada offer clinical breast examinations for women aged 40 and over and screening mammography every two years for women aged 50–69.^[12] In 2003, about 61% of women aged 50–69 in Canada reported having had a mammogram within the past two years.^[13]

The NHS Breast Screening Programme, the first of its kind in the world, began in 1988 and achieved national coverage in the mid-1990s, provides free breast cancer screening mammography every three years for all women in the UK aged 50 and over.^[14] As of March 31, 2006, 75.9% of women aged 53–64 resident in England had been screened at least once in the previous three years.^[15]

The Australian national breast screening program, BreastScreen Australia, was commenced in the early 1990s and invites women aged 50–69 to screening every 2 years. No routine clinical examination is performed, and the cost of screening is free to the point of diagnosis.

The Singapore national breast screening program, BreastScreen Singapore, is the only publicly funded national breast screening program in Asia, and enrolls women aged 50–64 for screening every two years. Like the Australian system, no clinical examination is performed routinely. Unlike most national screening systems however, clients have to pay half of the cost of the screening mammogram; this is in line with the Singapore health system's core principle of co-payment for all health services.

Criticisms

Some scientific groups however have expressed concern about the public's perceptions of the benefits of breast screening.^[16]

Data reported in the UK Million Woman Study indicates that if 134 mammograms are performed, 20 women will be called back for suspicious findings, and four biopsies will be necessary, to diagnose one cancer. Recall rates are higher in the U.S. than in the UK.^[17] The contribution of mammography to the early diagnosis of cancer is controversial, and for those found with benign lesions, mammography can create a high psychological and financial cost. For those diagnosed with cancer, mammography can be the difference between a lumpectomy versus metastatic disease.

Screening leads to false positive results and subsequent invasive procedures.^[18]

Nevertheless, surveys have shown that most women participating in mammography screening programs accept the risk of false positive recall and the majority do not find this highly distressing. The majority of women recalled will undergo additional imaging only, without any further intervention. There is some debate over how harmful such noninvasive recall assessment truly is.

A major effect of routine breast screening is to greatly increase the rate of early breast cancer detection, in particular for preinvasive ductal carcinoma in situ (DCIS), which is almost always impalpable and which cannot, for the most part, be detected reliably by any other test. While this ability to detect such very early breast malignancies is at the heart of claims that screening mammography can improve survival from breast cancer, it is also controversial. This is because a large percentage of such cases will almost certainly not progress to kill the patient, and thus mammography cannot be genuinely claimed to have been beneficial in such cases; in fact, it would lead to increased morbidity and unnecessary surgery for such patients.

It has thus been claimed that finding and treating many cases of DCIS represents "overdiagnosis" and "overtreatment". However, it is not possible to accurately predict which patients with DCIS will have an indolent nonfatal course, and which will inevitably progress to invasive cancer and death if left untreated. Consequently, all patients with DCIS are treated in much the same way, with at least wide local excision, and sometimes mastectomy if the DCIS is very extensive. The cure rate for DCIS if treated appropriately is extremely high. Thus, it can be argued that some women with DCIS detected by screening mammography do in fact benefit from screening, even if others do not. Any refinement of this therapeutic approach to breast malignancy requires further research and the development of methods that accurately predict the future cellular fate and biological behaviour of early cancers.

It is salient to note that the phenomenon of finding preinvasive malignancy or nonmalignant benign disease is commonplace in all forms of cancer screening, including pap smears for cervical cancer, fecal occult blood testing for colon cancer, and prostate-specific antigen testing for prostate cancer. All of these tests have the potential to detect very early malignancy before it becomes symptomatic, and to potentially lead to long term cure. All of them have false positives, and can lead to invasive procedures that may not benefit the patient.

Given current limitations in knowledge and technology, the only way to avoid "overdiagnosis" and "overtreatment", and to eliminate all harms inherent in breast cancer screening is not to screen at all, and thus to eliminate any benefit to at least some of the screened population that screening entails. In the case of breast cancer, cessation of screening would lead to an increase in the size and stage of breast cancers at diagnosis, since most cancers would only be detected when they become symptomatic.

Ultrasonography

Medical ultrasonography (Ultrasound) is a diagnostic aid to mammography.

Breast MRI

Magnetic resonance imaging (MRI) has been shown to detect cancers not visible on mammograms. The chief strength of breast MRI is its very high negative predictive value. A negative MRI can rule out the presence of cancer to a high degree of certainty, making it an excellent tool for screening in patients at high genetic risk or radiographically dense breasts, and for pre-treatment staging where the extent of disease is difficult to determine on mammography and ultrasound. MRI can diagnose benign proliferative change, fibroadenomas, and other common benign findings at a glance, often eliminating the need for costly and unnecessary biopsies or surgical procedures. The spatial and temporal resolution of breast MRI has increased markedly in recent years, making it possible to detect or rule out the presence of small *in situ* cancers, including ductal carcinoma in situ.

However, breast MRI has long been regarded to have disadvantages. For example, although it is 27–36% more sensitive, it has been claimed to be less specific than mammography.^[19] As a result, MRI studies may have more false positives (up to 30%), which may have undesirable financial and psychological costs. It is also a relatively expensive procedure, and one which requires the intravenous injection of gadolinium, which has been implicated in a rare reaction called nephrogenic systemic fibrosis. Although NSF is extremely uncommon, patients with a history of renal disease may not be able to undergo breast MRI. Further, an MRI may not be used for screening patients with a pacemaker or breast reconstruction patients with a tissue expander due to the presence of metal.

Proposed indications for using MRI for screening include:^[20]

- Strong family history of breast cancer
- Patients with BRCA-1 or BRCA-2 oncogene mutations
- Evaluation of women with breast implants
- History of previous lumpectomy or breast biopsy surgeries
- Axillary metastasis with an unknown primary tumor
- Very dense or scarred breast tissue

In addition, breast MRI may be helpful for screening in women who have had breast augmentation procedures involving intramammary injections of various foreign substances that may mask the appearances of breast cancer on mammography and/or ultrasound. These substances include:

- Silicone oil
- Polyacrylamide gel

Two studies published in 2007 demonstrated the strengths of MRI-based screening:

- In March 2007, an article published in the *New England Journal of Medicine* demonstrated that in 3.1% of patients with breast cancer, whose contralateral breast was clinically and mammographically tumor-free, MRI could detect breast cancer. Sensitivity for detection of breast cancer in this study was 91%, specificity 88%.^[21]
- In August 2007, an article published in *The Lancet* compared MRI breast cancer screening to conventional mammographic screening in 7,319 women. MRI screening was highly more sensitive (97% in the MRI group vs. 56% in the mammography group) in recognizing early high-grade Ductal Carcinoma in situ (DCIS), the most important precursor of invasive carcinoma. Despite the high sensitivity, MRI screening had a positive predictive value of 52%, which is totally accepted for cancer screening tests.^[22] The author of a comment published in the same issue of *The Lancet* concludes that "MRI outperforms mammography in tumour detection and diagnosis."^[23]

Based on this evidence, and the lack of effective alternative methods for screening in young women of very high genetic risk (either an extremely strong first degree family history or proven BRCA1 or BRCA2 oncogene mutation carrier status) for breast cancer, the Australian federal government decided to routinely reimburse annual breast MRI scans for such women under the age of 50 from January 2009 onwards.

BRCA testing

A clinical practice guideline by the US Preventive Services Task Force :^[24]

- "recommends against routine referral for genetic counseling or routine breast cancer susceptibility gene (BRCA) testing for women whose family history is not associated with an increased risk for deleterious mutations in breast cancer susceptibility gene 1 (BRCA1) or breast cancer susceptibility gene 2 (BRCA2)" The Task Force gave a grade D recommendation.^[25]
- "recommends that women whose family history is associated with an increased risk for deleterious mutations in BRCA1 or BRCA2 genes be referred for genetic counseling and evaluation for BRCA testing." The Task Force gave a grade B recommendation.^[25]

The Task Force noted that about 2% of women have family histories that indicate increased risk as defined by:

- For non–Ashkenazi Jewish women, any of the following:
 - "2 first-degree relatives with breast cancer, 1 of whom received the diagnosis at age 50 years or younger"
 - "3 or more first- or second-degree relatives with breast cancer regardless of age at diagnosis"
 - "both breast and ovarian cancer among first- and second- degree relatives"
 - "a first-degree relative with bilateral breast cancer"
 - "a combination of 2 or more first- or second-degree relatives with ovarian cancer regardless of age at diagnosis"

- "a first- or second-degree relative with both breast and ovarian cancer at any age"
- "a history of breast cancer in a male relative."
- "For women of Ashkenazi Jewish heritage, an increased-risk family history includes any first-degree relative (or 2 second-degree relatives on the same side of the family) with breast or ovarian cancer."

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External links

- Breastcancer.org (<http://www.breastcancer.org>), US non-profit information provider
- Breast cancer (http://www.dmoz.org/Health/Conditions_and_Diseases/Cancer/Breast/) at the Open Directory Project
- Breast cancer screening page (<http://www.cancer.gov/cancertopics/screening/Breast>) from the National Cancer Institute
- Breast Cancer Screening (<http://healthtools.aarp.org/galecontent/breast-cancer-screening>) from AARP.org

Fourier transform spectroscopy

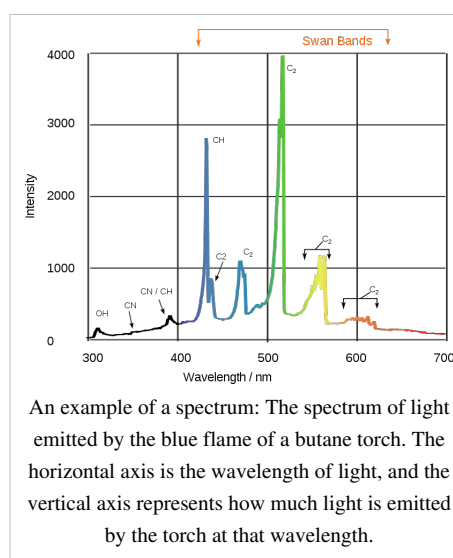
Fourier transform spectroscopy is a measurement technique whereby spectra are collected based on measurements of the coherence of a radiative source, using time-domain or space-domain measurements of the electromagnetic radiation or other type of radiation. It can be applied to a variety of types of spectroscopy including optical spectroscopy, infrared spectroscopy (FTIR, FT-NIRS), nuclear magnetic resonance (NMR) and magnetic resonance spectroscopic imaging (MRSI)^[1], mass spectrometry and electron spin resonance spectroscopy. There are several methods for measuring the temporal coherence of the light (see: field-autocorrelation), including the continuous wave *Michelson* or *Fourier transform* spectrometer and the pulsed Fourier transform spectrograph (which is more sensitive and has a much shorter sampling time than conventional spectroscopic techniques, but is only applicable in a laboratory environment).

The term *Fourier transform spectroscopy* reflects the fact that in all these techniques, a Fourier transform is required to turn the raw data into the actual spectrum, and in many of the cases in optics involving interferometers, is based on the Wiener–Khinchin theorem.

Conceptual introduction

Measuring an emission spectrum

One of the most basic tasks in spectroscopy is to characterize the spectrum of a light source: How much light is emitted at each different wavelength. The most straightforward way to measure a spectrum is to pass the light through a monochromator, an instrument that blocks all of the light *except* the light at a certain wavelength (the un-blocked wavelength is set by a knob on the monochromator). Then the intensity of this remaining (single-wavelength) light is measured. The measured intensity directly indicates how much light is emitted at that wavelength. By varying the monochromator's wavelength setting, the full spectrum can be measured. This simple scheme in fact describes how *some* spectrometers work.



Fourier transform spectroscopy is a less intuitive way to get the same information. Rather than allowing only one wavelength at a time to pass through to the detector, this technique lets through a beam containing many different wavelengths of light at once, and measures the *total* beam intensity. Next, the beam is modified to contain a *different* combination of wavelengths, giving a second data point. This process is repeated many times. Afterwards, a computer takes all this data and works backwards to infer how much light there is at each wavelength.

To be more specific, between the light source and the detector, there is a certain configuration of mirrors that allows some wavelengths to pass through but blocks others (due to wave interference). The beam is modified for each new data point by moving one of the mirrors; this changes the set of wavelengths that can pass through.

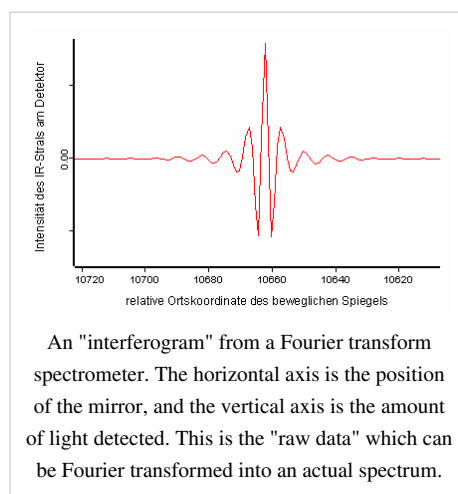
As mentioned, computer processing is required to turn the raw data (light intensity for each mirror position) into the desired result (light intensity for each wavelength). The processing required turns out to be a common algorithm called the Fourier transform (hence the name, "Fourier transform spectroscopy"). The raw data is sometimes called an "interferogram".

Measuring an absorption spectrum

The method of Fourier transform spectroscopy can also be used for absorption spectroscopy. The primary example is "FTIR Spectroscopy", a common technique in chemistry.

In general, the goal of absorption spectroscopy is to measure how well a sample absorbs or transmits light at each different wavelength. Although absorption spectroscopy and emission spectroscopy are different in principle, they are closely related in practice; any technique for emission spectroscopy can also be used for absorption spectroscopy. First, the emission spectrum of a broadband lamp is measured (this is called the "background spectrum"). Second, the emission spectrum of the same lamp *shining through the sample* is measured (this is called the "sample spectrum"). The sample will absorb some of the light, causing the spectra to be different. The ratio of the "sample spectrum" to the "background spectrum" is directly related to the sample's absorption spectrum.

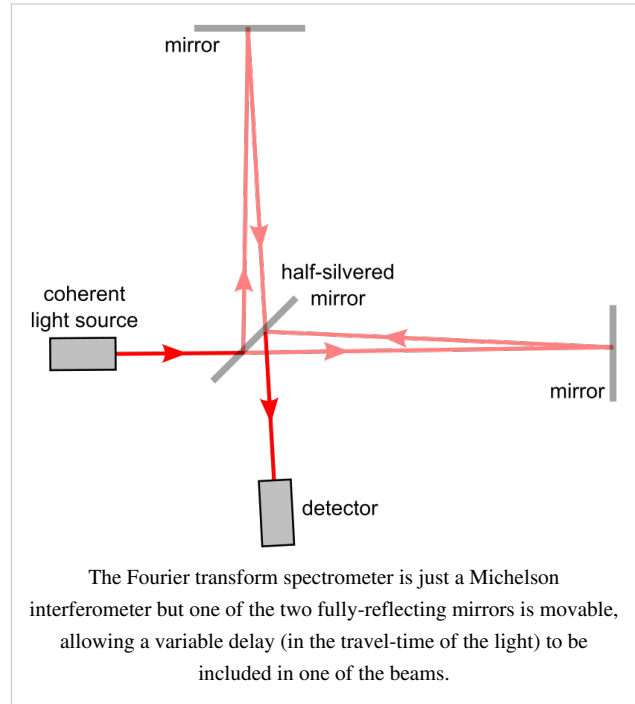
Accordingly, the technique of "Fourier transform spectroscopy" can be used both for measuring emission spectra (for example, the emission spectrum of a star), *and* absorption spectra (for example, the absorption spectrum of a glass of liquid).



Continuous wave *Michelson* or *Fourier transform* spectrograph

The Michelson spectrograph is similar to the instrument used in the Michelson-Morley experiment. Light from the source is split into two beams by a half-silvered mirror, one is reflected off a fixed mirror and one off a moving mirror which introduces a time delay—the Fourier transform spectrometer is just a Michelson interferometer with a movable mirror. The beams interfere, allowing the temporal coherence of the light to be measured at each different time delay setting, effectively converting the time domain into a spatial coordinate. By making measurements of the signal at many discrete positions of the moving mirror, the spectrum can be reconstructed using a Fourier transform of the temporal coherence of the light. Michelson spectrographs are capable of very high spectral resolution observations of very bright sources. The Michelson or Fourier transform spectrograph was popular for infra-red applications at a time when infra-red astronomy only had single pixel detectors.

Imaging Michelson spectrometers are a possibility, but in general have been supplanted by imaging Fabry–Pérot instruments which are easier to construct.



Extracting the spectrum

The intensity as a function of the path length difference in the interferometer p and wavenumber $\tilde{\nu} = 1/\lambda$ is ^[2]

$$I(p, \tilde{\nu}) = I(\tilde{\nu})[1 + \cos(2\pi\tilde{\nu}p)],$$

where $I(\tilde{\nu})$ is the spectrum to be determined. Note that it is not necessary for $I(\tilde{\nu})$ to be modulated by the sample before the interferometer. In fact, most FTIR spectrometers place the sample after the interferometer in the optical path. The total intensity at the detector is

$$I(p) = \int_0^\infty I(p, \tilde{\nu}) d\tilde{\nu} = \int_0^\infty I(\tilde{\nu})[1 + \cos(2\pi\tilde{\nu}p)] d\tilde{\nu}.$$

This is just a Fourier cosine transform. The inverse gives us our desired result in terms of the measured quantity $I(p)$:

$$I(\tilde{\nu}) = 4 \int_0^\infty [I(p) - \frac{1}{2}I(p=0)] \cos(2\pi\tilde{\nu}p) dp.$$

Pulsed *Fourier transform* spectrometer

A pulsed *Fourier transform* spectrometer does not employ transmittance techniques. In the most general description of pulsed FT spectrometry, a sample is exposed to an energizing event which causes a periodic response. The frequency of the periodic response, as governed by the field conditions in the spectrometer, is indicative of the measured properties of the analyte.

Examples of pulsed Fourier transform spectrometry

In magnetic spectroscopy (EPR, NMR), an RF pulse in a strong ambient magnetic field is used as the energizing event. This turns the magnetic particles at an angle to the ambient field, resulting in gyration. The gyrating spins then induce a periodic current in a detector coil. Each spin exhibits a characteristic frequency of gyration (relative to the field strength) which reveals information about the analyte.

In Fourier transform mass spectrometry, the energizing event is the injection of the charged sample into the strong electromagnetic field of a cyclotron. These particles travel in circles, inducing a current in a fixed coil on one point in their circle. Each traveling particle exhibits a characteristic cyclotron frequency-field ratio revealing the masses in the sample.

Free induction decay

Pulsed FT spectrometry gives the advantage of requiring a single, time-dependent measurement which can easily deconvolute a set of similar but distinct signals. The resulting composite signal, is called a *free induction decay*, because typically the signal will decay due to inhomogeneities in sample frequency, or simply unrecoverable loss of signal due to entropic loss of the property being measured.

Stationary forms of Fourier transform spectrometers

In addition to the scanning forms of Fourier transform spectrometers, there are a number of stationary or self-scanned forms.^[3] While the analysis of the interferometric output is similar to that of the typical scanning interferometer, significant differences apply, as shown in the published analyses. Some stationary forms retain the Fellgett multiplex advantage, and their use in the spectral region where detector noise limits apply is similar to the scanning forms of the FTS. In the photon-noise limited region, the application of stationary interferometers is dictated by specific consideration for the spectral region and the application.

Fellgett advantage

One of the most important advantages of Fourier transform spectroscopy was shown by P.B. Fellgett, an early advocate of the method. The Fellgett advantage, also known as the multiplex principle, states that when obtaining a spectrum when measurement noise is dominated by detector noise, a multiplex spectrometer such as a Fourier transform spectrometer will produce a relative improvement in signal-to-noise ratio, compared to an equivalent scanning monochromator, of the order of the square root of m , where m is the number of sample points comprising the spectrum.

Converting spectra from time domain to frequency domain

$$S(t) = \int_{-\infty}^{\infty} I(\nu) e^{-i\nu 2\pi t} d\nu$$

The sum is performed over all contributing frequencies to give a signal $S(t)$ in the time domain.

$$I(\nu) = \int_{-\infty}^{\infty} S(t) e^{i\nu 2\pi t} dt$$

gives non-zero value when $S(t)$ contains a component that matches the oscillating function.

Remember that

$$e^{ix} = \cos x + i \sin x$$

See also

- Applied spectroscopy
- Forensic chemistry
- Forensic polymer engineering
- Nuclear Magnetic Resonance
- Infrared spectroscopy

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- [3] William H. Smith U.S. Patent 4976542 (<http://www.google.com/patents?vid=4976542>) Digital Array Scanned Interferometer, issued Dec. 11, 1990

External links

- Description of how a Fourier transform spectrometer works (<http://scienceworld.wolfram.com/physics/FourierTransformSpectrometer.html>)
- The Michelson or Fourier transform spectrograph (<http://www.astro.livjm.ac.uk/courses/phys362/notes/>)
- Internet Journal of Vibrational Spectroscopy - How FTIR works (<http://www.ijvs.com/volume5/edition5/section1.html#Feature>)
- Fourier Transform Spectroscopy Topical Meeting and Tabletop Exhibit (<http://www.osa.org/meetings/topicalmeetings/fts/default.aspx>)

FT-Near Infrared Spectroscopy and Imaging

Fourier transform infrared spectroscopy (FTIR)^[1] is a technique which is used to obtain an infrared spectrum of absorption, emission, photoconductivity or Raman scattering of a solid, liquid or gas. An FTIR spectrometer simultaneously collects spectral data in a wide spectral range. This confers a significant advantage over a dispersive spectrometer which measures intensity over a narrow range of wavelengths at a time. FTIR technique has made dispersive infrared spectrometers all but obsolete (except sometimes in the near infrared) and opened up new applications of infrared spectroscopy.

The term *Fourier transform infrared spectroscopy* originates from the fact that a Fourier transform (a mathematical algorithm) is required to convert the raw data into the actual spectrum. For other uses of this kind of technique, see Fourier transform spectroscopy.

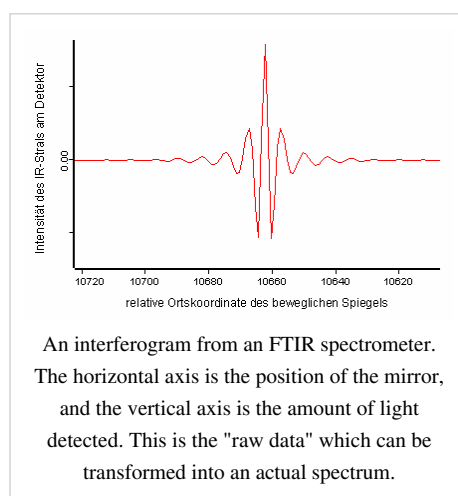
Conceptual introduction

The goal of any absorption spectroscopy (FTIR, ultraviolet-visible ("UV-Vis") spectroscopy, etc.) is to measure how well a sample absorbs light at each wavelength. The most straightforward way to do this, the "dispersive spectroscopy" technique, is to shine a monochromatic light beam at a sample, measure how much of the light is absorbed, and repeat for each different wavelength. (This is how UV-Vis spectrometers work, for example.)

Fourier transform spectroscopy is a less intuitive way to obtain the same information. Rather than shining a *monochromatic* beam of light at the sample, this technique shines a beam containing many different frequencies of light at once, and measures how much of that beam is absorbed by the sample. Next, the beam is modified to contain a different combination of frequencies, giving a second data point. This process is repeated many times. Afterwards, a computer takes all this data and works backwards to infer what the absorption is at each wavelength.

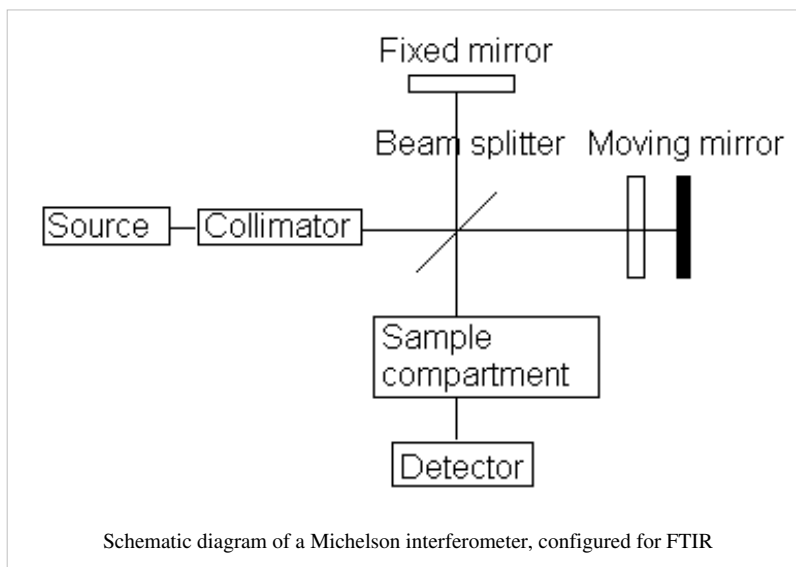
The beam described above is generated by starting with a broadband light source—one containing the full spectrum of wavelengths to be measured. The light shines into a certain configuration of mirrors, called a Michelson interferometer, that allows some wavelengths to pass through but blocks others (due to wave interference). The beam is modified for each new data point by moving one of the mirrors; this changes the set of wavelengths that pass through.

As mentioned, computer processing is required to turn the raw data (light absorption for each mirror position) into the desired result (light absorption for each wavelength). The processing required turns out to be a common algorithm called the Fourier transform (hence the name, "Fourier transform spectroscopy"). The raw data is sometimes called an "interferogram".



Michelson interferometer

In a Michelson interferometer adapted for FTIR, light from the polychromatic infrared source, approximately a black-body radiator, is collimated and directed to a beam splitter. Ideally 50% of the light is reflected towards the fixed mirror and 50% is transmitted towards the moving mirror. Light is reflected from the two mirrors back to the beam splitter and (ideally) 50% of the original light passes into the sample compartment. There, the light is focussed on the sample. On leaving the sample compartment the light is refocused on to the detector. The



difference in optical path length between the two arms to the interferometer is known as the retardation. An interferogram is obtained by varying the retardation and recording the signal from the detector for various values of the retardation. The form of the interferogram when no sample is present depends on factors such as the variation of source intensity and splitter efficiency with wavelength. This results in a maximum at zero retardation, when there is constructive interference at all wavelengths, followed by series of "wiggles". The position of zero retardation is determined accurately by finding the point of maximum intensity in the interferogram. When a sample is present the background interferogram is modulated by the presence of absorption bands in the sample.

There are two principle advantages for a FT spectrometer compared to a scanning (dispersive) spectrometer.^{[2] [3]}

1. The multiplex or Fellgett's advantage. This arises from the fact that information from all wavelengths is collected simultaneously. It results in a higher Signal-to-noise ratio for a given scan-time or a shorter scan-time for a given resolution.
2. The throughput or Jacquinot's advantage. This results from the fact that, in a dispersive instrument, the monochromator has entrance and exit slits which restrict the amount of light that passes through it. The interferometer throughput is determined only by the diameter of the collimated beam coming from the source.

Other minor advantages include less sensitivity to stray light,^[3] and "Connes' advantage" (better wavelength accuracy)^[3], while a disadvantage is that FTIR cannot use the advanced electronic filtering techniques that often makes its signal-to-noise ratio inferior to that of dispersive measurements.^[3]

Resolution

The interferogram belongs in the length domain. Fourier transform (FT) inverts the dimension, so the FT of the interferogram belongs in the reciprocal length domain, that is the wavenumber domain. The spectral resolution in wavenumbers per cm is equal to the reciprocal of the maximum retardation in cm. Thus a 4 cm^{-1} resolution will be obtained if the maximum retardation is 0.25 cm; this is typical of the cheaper FTIR instruments. Much higher resolution can be obtained by increasing the maximum retardation. This is not easy as the moving mirror must travel in a near-perfect straight line. The use of corner-cube mirrors in place of the flat mirrors is helpful as an outgoing ray from a corner-cube mirror is parallel to the incoming ray, regardless of the orientation of the mirror about axes perpendicular to the axis of the light beam. Connes measured in 1966 the temperature of the atmosphere of Venus by recording the vibration-rotation spectrum of Venusian CO_2 at 0.1 cm^{-1} resolution.^[4] Michelson himself attempted to resolve the hydrogen H_α emission band in the spectrum of a hydrogen atom into its two components by using his

interferometer.^{[1] p25} A spectrometer with 0.001 cm^{-1} resolution is now available commercially from Bruker. The throughput advantage is important for high-resolution FTIR as the monochromator in a dispersive instrument with the same resolution would have very narrow entrance and exit slits.

Beam splitter

The beam-splitter can not be made of a common glass, as it is opaque to infrared radiation of wavelengths longer than about $2.5\text{ }\mu\text{m}$. A thin film, usually of a plastic material, is used instead. However, as any material has a limited range of optical transmittance, several beam-splitters are used interchangeably to cover a wide spectral range.

Fourier transform

The interferogram in practice consists of a set of intensities measured for discrete values of retardation. The difference between successive retardation values is constant. Thus, a discrete Fourier transform is needed. The fast Fourier transform (FFT) algorithm is used.

Far-infrared FTIR

The first FTIR spectrometers were developed for far-infrared range. The reason for this has to do with the mechanical tolerance needed for good optical performance, which is related to the wavelength of the light being used. For the relatively long wavelengths of the far infrared ($\sim 10\text{ }\mu\text{m}$), tolerances are adequate, whereas for the rock-salt region tolerances have to be better than $1\text{ }\mu\text{m}$. A typical instrument was the cube interferometer developed at the NPL^[5] and marketed by Grubb Parsons. It used a stepper motor to drive the moving mirror, recording the detector response after each step was completed.

Mid-infrared FTIR

With the advent of cheap microcomputers it became possible to have a computer dedicated to controlling the spectrometer, collecting the data, doing the Fourier transform and presenting the spectrum. This provided the impetus for the development of FTIR spectrometers for the rock-salt region. The problems of manufacturing ultra-high precision optical and mechanical components had to be solved. A wide range of instrument is now available commercially. Although instrument design has become more sophisticated, the basic principles remain the same. Nowadays, the moving mirror of the interferometer moves at a constant velocity, and sampling of the interferogram is triggered by finding zero-crossings in the fringes of a secondary interferometer lit by a helium-neon laser. This confers high wavenumber accuracy on the resulting infrared spectrum and avoids wavenumber calibration errors.

Near-infrared FTIR

The near-infrared region spans the wavelength range between the rock-salt region and the start of the visible region at about 750 nm . Overtones of fundamental vibrations can be observed in this region. It is used mainly in industrial applications such as process control.

Applications

FTIR can be used in all applications where a dispersive spectrometer was used in the past (see external links). In addition, the multiplex and throughput advantages have opened up new areas of application. These include:

- GC-IR (gas chromatography-infrared spectrometry). A gas chromatograph can be used to separate the components of a mixture. The fractions containing single components are directed into an FTIR spectrometer, to provide the infrared spectrum of the sample. This technique is complementary to GC-MS (gas

chromatography-mass spectrometry). The GC-IR method is particularly useful for identifying isomers, which by their nature have identical masses. The key to the successful use of GC-IR is that the interferogram can be captured in a very short time, typically less than 1 second. FTIR has also been applied to the analysis of liquid chromatography fractions.^[3]

- TG-IR (thermogravimetry-infrared spectrometry) IR spectra of the gases evolved during thermal decomposition are obtained as a function of temperature.^[6]
- Micro-samples. Tiny samples, such as in forensic analysis, can be examined with the aid of an infrared microscope in the sample chamber. An image of the surface can be obtained by scanning.^[7] Another example is the use of FTIR to characterize artistic materials in old-master paintings.^[8]
- Emission spectra. Instead of recording the spectrum of light transmitted through the sample, FTIR spectrometer can be used to acquire spectrum of light emitted by the sample. Such emission could be induced by various processes, and the most common ones are luminescence and Raman scattering. Little modification is required to an absorption FTIR spectrometer to record emission spectra and therefore many commercial FTIR spectrometers combine both absorption and emission/Raman modes.^[9]
- Photocurrent spectra. This mode uses a standard, absorption FTIR spectrometer. The studied sample is placed instead of the FTIR detector, and its photocurrent, induced by the spectrometer's broadband source, is used to record the interferogram, which is then converted into the photoconductivity spectrum of the sample.^[10]

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External links

- Infracord spectrometer (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC441765/pdf/jcinvest00449-0191.pdf>) photograph
- The Grubb-Parsons-NPL cube interferometer Spectroscopy, part 2 by Dudley Williams, page 81 (http://books.google.co.uk/books?id=XTolQEkzSR0C&pg=PA93&lpg=PA93&dq=grubb+parsons+cube&source=bl&ots=l0Sm8klxHG&sig=SzKdjgTB8YPyitRgAAIwH2zIOlo&hl=en&ei=w6lRTM-BNYaD4QaC48ygAw&sa=X&oi=book_result&ct=result&resnum=9&ved=0CDgQ6AEwCA#v=onepage&q=grubb+parsons+cube&f=false)
- FTIR application notes (<http://las.perkinelmer.com/Catalog/TechLibDetails.htm?expand=Application&20Notes&ObjectId=FTIR+&+FTNIR+Spectrometers&CategoryId=FTIR+&+FTNIR+Spectrometers&type=CATEGORY>) from Perkin Elmer

- FTIR application notes (<http://www.varianinc.com/cgi-bin/nav?applications/ftir&cid=LNHOMKLFPQ>) from Varian
- Infrared / FTIR Application Notes (<http://www.selectscience.net/infrared-+-ftir/application-notes>) Recent publications.
- Semiconductor applications (<http://www.piketech.com/technical/application-pdfs/SemiconductorApplOverview.pdf>) FTIR Sampling Techniques Overview.
- infrared materials (<http://infrared.als.lbl.gov/content/web-links/58-irwindows>) Properties of many salt crystals and useful links.

Chemical imaging

Chemical imaging (as quantitative - *chemical mapping*) is the analytical capability to create a visual image of components distribution from simultaneous measurement of spectra and spatial, time informations.^{[1] [2]}

The main idea - for chemical imaging, the analyst may choose to take as many data spectrum measured at a particular chemical component in spatial location at time; this is useful for chemical identification and quantification. Alternatively, selecting an image plane at a particular data spectrum (PCA - multivariable data of wavelength, spatial location at time) can map the spatial distribution of sample components, provided that their spectral signatures are different at the selected data spectrum.

Software for chemical imaging is most specific and distinguished from chemical methods as the chemometrics.

Imaging technique is most often applied to either solid or gel samples, and has applications in chemistry, biology^{[3] [4] [5] [6] [7] [8]}, medicine^{[9] [10]}, pharmacy^[11] (see also for example: Chemical Imaging Without Dyeing^[12]), food science, biotechnology^{[13] [14]}, agriculture and industry (see for example: NIR Chemical Imaging in Pharmaceutical Industry^[15] and Pharmaceutical Process Analytical Technology: ^[16]). NIR, IR and Raman chemical imaging is also referred to as hyperspectral, spectroscopic, spectral or multispectral imaging (also see microspectroscopy). However, other ultra-sensitive and selective imaging techniques are also in use that involve either UV-visible or fluorescence microspectroscopy. Many imaging techniques can be used to analyze samples of all sizes, from the single molecule^{[17] [18]} to the cellular level in biology and medicine^{[19] [20] [21]}, and to images of planetary systems in astronomy, but different instrumentation is employed for making observations on such widely different systems.

Imaging instrumentation is composed of three components: a radiation source to illuminate the sample, a spectrally selective element, and usually a detector array (the camera) to collect the images. When many stacked spectral channels (wavelengths) are collected for different locations of the microspectrometer focus on a line or planar array in the focal plane, the data is called hyperspectral; fewer wavelength data sets are called multispectral. The data format is called a hypercube. The data set may be visualized as a three-dimensional block of data spanning two spatial dimensions (x and y), with a series of wavelengths (λ) making up the third (spectral) axis. The hypercube can be visually and mathematically treated as a series of spectrally resolved images (each image plane corresponding to the image at one wavelength) or a series of spatially resolved spectra.

Many materials, both manufactured and naturally occurring, derive their functionality from the spatial distribution of sample components. For example, extended release pharmaceutical formulations can be achieved by using a coating that acts as a barrier layer. The release of active ingredient is controlled by the presence of this barrier, and imperfections in the coating, such as discontinuities, may result in altered performance. In the semi-conductor industry, irregularities or contaminants in silicon wafers or printed micro-circuits can lead to failure of these components. The functionality of biological systems is also dependent upon chemical gradients – a single cell, tissue, and even whole organs function because of the very specific arrangement of components. It has been shown that even small changes in chemical composition and distribution may be an early indicator of disease.

Any material that depends on chemical gradients for functionality may be amenable to study by an analytical technique that couples spatial and chemical characterization. To efficiently and effectively design and manufacture such materials, the 'what' and the 'where' must both be measured. The demand for this type of analysis is increasing as manufactured materials become more complex. Chemical imaging techniques is critical to understanding modern manufactured products and in some cases is a non-destructive technique so that samples are preserved for further testing.

History

Commercially available laboratory-based chemical imaging systems emerged in the early 1990s (ref. 1-5). In addition to economic factors, such as the need for sophisticated electronics and extremely high-end computers, a significant barrier to commercialization of infrared imaging was that the focal plane array (FPA) needed to read IR images were not readily available as commercial items. As high-speed electronics and sophisticated computers became more commonplace, and infrared cameras became readily commercially available, laboratory chemical imaging systems were introduced.

Initially used for novel research in specialized laboratories, chemical imaging became a more commonplace analytical technique used for general R&D, quality assurance (QA) and quality control (QC) in less than a decade. The rapid acceptance of the technology in a variety of industries (pharmaceutical, polymers, semiconductors, security, forensics and agriculture) rests in the wealth of information characterizing both chemical composition and morphology. The parallel nature of chemical imaging data makes it possible to analyze multiple samples simultaneously for applications that require high throughput analysis in addition to characterizing a single sample.

Principles

Chemical imaging shares the fundamentals of vibrational spectroscopic techniques, but provides additional information by way of the simultaneous acquisition of spatially resolved spectra. It combines the advantages of digital imaging with the attributes of spectroscopic measurements. Briefly, vibrational spectroscopy measures the interaction of light with matter. Photons that interact with a sample are either absorbed or scattered; photons of specific energy are absorbed, and the pattern of absorption provides information, or a fingerprint, on the molecules that are present in the sample.

On the other hand, in terms of the observation setup, chemical imaging can be carried out in one of the following modes: (optical) absorption, emission (fluorescence), (optical) transmission or scattering (Raman). A consensus currently exists that the fluorescence (emission) and Raman scattering modes are the most sensitive and powerful, but also the most expensive.

In a transmission measurement, the radiation goes through a sample and is measured by a detector placed on the far side of the sample. The energy transferred from the incoming radiation to the molecule(s) can be calculated as the difference between the quantity of photons that were emitted by the source and the quantity that is measured by the detector. In a diffuse reflectance measurement, the same energy difference measurement is made, but the source and detector are located on the same side of the sample, and the photons that are measured have re-emerged from the illuminated side of the sample rather than passed through it. The energy may be measured at one or multiple wavelengths; when a series of measurements are made, the response curve is called a spectrum.

A key element in acquiring spectra is that the radiation must somehow be energy selected – either before or after interacting with the sample. Wavelength selection can be accomplished with a fixed filter, tunable filter, spectrograph, an interferometer, or other devices. For a fixed filter approach, it is not efficient to collect a significant number of wavelengths, and multispectral data are usually collected. Interferometer-based chemical imaging requires that entire spectral ranges be collected, and therefore results in hyperspectral data. Tunable filters have the flexibility to provide either multi- or hyperspectral data, depending on analytical requirements.

Spectra may be measured one point at a time using a single element detector (single-point mapping), as a line-image using a linear array detector (typically 16 to 28 pixels) (linear array mapping), or as a two-dimensional image using a Focal Plane Array (FPA)(typically 256 to 16,384 pixels) (FPA imaging). For single-point the sample is moved in the x and y directions point-by-point using a computer-controlled stage. With linear array mapping, the sample is moved line-by-line with a computer-controlled stage. FPA imaging data are collected with a two-dimensional FPA detector, hence capturing the full desired field-of-view at one time for each individual wavelength, without having to move the sample. FPA imaging, with its ability to collect tens of thousands of spectra simultaneously is orders of magnitude faster than linear arrays which can typically collect 16 to 28 spectra simultaneously, which are in turn much faster than single-point mapping.

Terminology

Some words common in spectroscopy, optical microscopy and photography have been adapted or their scope modified for their use in chemical imaging. They include: resolution, field of view and magnification. There are two types of resolution in chemical imaging. The spectral resolution refers to the ability to resolve small energy differences; it applies to the spectral axis. The spatial resolution is the minimum distance between two objects that is required for them to be detected as distinct objects. The spatial resolution is influenced by the field of view, a physical measure of the size of the area probed by the analysis. In imaging, the field of view is a product of the magnification and the number of pixels in the detector array. The magnification is a ratio of the physical area of the detector array divided by the area of the sample field of view. Higher magnifications for the same detector image a smaller area of the sample.

Types of vibrational chemical imaging instruments

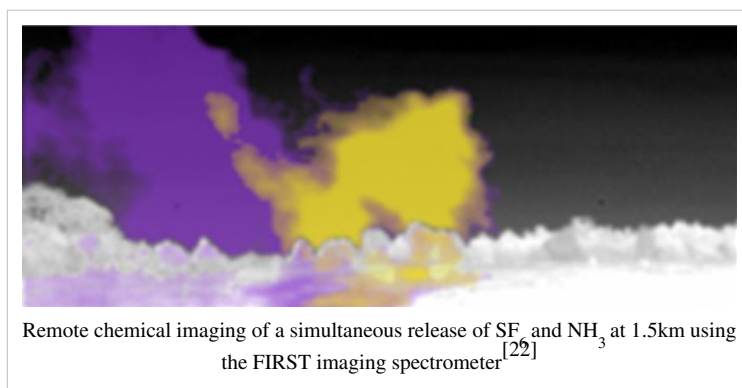
Chemical imaging has been implemented for mid-infrared, near-infrared spectroscopy and Raman spectroscopy. As with their bulk spectroscopy counterparts, each imaging technique has particular strengths and weaknesses, and are best suited to fulfill different needs.

Mid-infrared chemical imaging

Mid-infrared (MIR) spectroscopy probes fundamental molecular vibrations, which arise in the spectral range 2,500-25,000 nm. Commercial imaging implementations in the MIR region typically employ Fourier Transform Infrared (FT-IR) interferometers and the range is more commonly presented in wavenumber, $4,000 - 400 \text{ cm}^{-1}$. The MIR absorption bands tend to be relatively narrow and well-resolved; direct spectral interpretation is often possible by an experienced spectroscopist. MIR spectroscopy can distinguish subtle changes in chemistry and structure, and is often used for the identification of unknown materials. The absorptions in this spectral range are relatively strong; for this reason, sample presentation is important to limit the amount of material interacting with the incoming radiation in the MIR region. Most data collected in this range is collected in transmission mode through thin sections (~10 micrometres) of material. Water is a very strong absorber of MIR radiation and wet samples often require advanced sampling procedures (such as attenuated total reflectance). Commercial instruments include point and line mapping, and imaging. All employ an FT-IR interferometer as wavelength selective element and light source.

For types of MIR microscope, see [Microscopy#Infrared microscopy](#).

Atmospheric windows in the infrared spectrum are also employed to perform chemical imaging remotely. In these spectral regions the atmospheric gases (mainly water and CO_2) present low absorption and allow infrared viewing over kilometer distances. Target molecules can then be viewed using the selective absorption/emission processes described above. An example of the chemical imaging of a simultaneous release of SF_6 and NH_3 is shown in the image.



Near-infrared chemical imaging

The analytical near infrared (NIR) region spans the range from approximately 700-2,500 nm. The absorption bands seen in this spectral range arise from overtones and combination bands of O-H, N-H, C-H and S-H stretching and bending vibrations. Absorption is one to two orders of magnitude smaller in the NIR compared to the MIR; this phenomenon eliminates the need for extensive sample preparation. Thick and thin samples can be analyzed without any sample preparation, it is possible to acquire NIR chemical images through some packaging materials, and the technique can be used to examine hydrated samples, within limits. Intact samples can be imaged in transmittance or diffuse reflectance.

The lineshapes for overtone and combination bands tend to be much broader and more overlapped than for the fundamental bands seen in the MIR. Often, multivariate methods are used to separate spectral signatures of sample components. NIR chemical imaging is particularly useful for performing rapid, reproducible and non-destructive analyses of known materials^{[23] [24]}. NIR imaging instruments are typically based on one of two platforms: imaging using a tunable filter and broad band illumination, and line mapping employing an FT-IR interferometer as the wavelength filter and light source.

Raman chemical imaging

The Raman shift chemical imaging spectral range spans from approximately 50 to 4,000 cm^{-1} ; the actual spectral range over which a particular Raman measurement is made is a function of the laser excitation frequency. The basic principle behind Raman spectroscopy differs from the MIR and NIR in that the x-axis of the Raman spectrum is measured as a function of energy shift (in cm^{-1}) relative to the frequency of the laser used as the source of radiation. Briefly, the Raman spectrum arises from inelastic scattering of incident photons, which requires a change in polarizability with vibration, as opposed to infrared absorption, which requires a change in dipole moment with vibration. The end result is spectral information that is similar and in many cases complementary to the MIR. The Raman effect is weak - only about one in 10^7 photons incident to the sample undergoes Raman scattering. Both organic and inorganic materials possess a Raman spectrum; they generally produce sharp bands that are chemically specific. Fluorescence is a competing phenomenon and, depending on the sample, can overwhelm the Raman signal, for both bulk spectroscopy and imaging implementations.

Raman chemical imaging requires little or no sample preparation. However, physical sample sectioning may be used to expose the surface of interest, with care taken to obtain a surface that is as flat as possible. The conditions required for a particular measurement dictate the level of invasiveness of the technique, and samples that are sensitive to high power laser radiation may be damaged during analysis. It is relatively insensitive to the presence of water in the sample and is therefore useful for imaging samples that contain water such as biological material.

Fluorescence imaging (visible and NIR)

This emission microspectroscopy mode is the most sensitive in both visible and FT-NIR microspectroscopy, and has therefore numerous biomedical, biotechnological and agricultural applications. There are several powerful, highly specific and sensitive fluorescence techniques that are currently in use, or still being developed; among the former are FLIM, FRAP, FRET and FLIM-FRET; among the latter are NIR fluorescence and probe-sensitivity enhanced NIR fluorescence microspectroscopy and nanospectroscopy techniques (see "Further reading" section).

Sampling and samples

The value of imaging lies in the ability to resolve spatial heterogeneities in solid-state or gel/gel-like samples. Imaging a liquid or even a suspension has limited use as constant sample motion serves to average spatial information, unless ultra-fast recording techniques are employed as in fluorescence correlation microspectroscopy or FLIM observations where a single molecule may be monitored at extremely high (photon) detection speed. High-throughput experiments (such as imaging multi-well plates) of liquid samples can however provide valuable information. In this case, the parallel acquisition of thousands of spectra can be used to compare differences between samples, rather than the more common implementation of exploring spatial heterogeneity within a single sample.

Similarly, there is no benefit in imaging a truly homogeneous sample, as a single point spectrometer will generate the same spectral information. Of course the definition of homogeneity is dependent on the spatial resolution of the imaging system employed. For MIR imaging, where wavelengths span from 3-10 micrometres, objects on the order of 5 micrometres may theoretically be resolved. The sampled areas are limited by current experimental implementations because illumination is provided by the interferometer. Raman imaging may be able to resolve particles less than 1 micrometre in size, but the sample area that can be illuminated is severely limited. With Raman imaging, it is considered impractical to image large areas and, consequently, large samples. FT-NIR chemical/hyperspectral imaging usually resolves only larger objects (>10 micrometres), and is better suited for large samples because illumination sources are readily available. However, FT-NIR microspectroscopy was recently reported to be capable of about 1.2 micron (micrometer) resolution in biological samples^[25] Furthermore, two-photon excitation FCS experiments were reported to have attained 15 nanometer resolution on biomembrane thin films with a special coincidence photon-counting setup.

Detection limit

The concept of the detection limit for chemical imaging is quite different than for bulk spectroscopy, as it depends on the sample itself. Because a bulk spectrum represents an average of the materials present, the spectral signatures of trace components are simply overwhelmed by dilution. In imaging however, each pixel has a corresponding spectrum. If the physical size of the trace contaminant is on the order of the pixel size imaged on the sample, its spectral signature will likely be detectable. If however, the trace component is dispersed homogeneously (relative to pixel image size) throughout a sample, it will not be detectable. Therefore, detection limits of chemical imaging techniques are strongly influenced by particle size, the chemical and spatial heterogeneity of the sample, and the spatial resolution of the image.

Data analysis

Data analysis methods for chemical imaging data sets typically employ mathematical algorithms common to single point spectroscopy or to image analysis. The reasoning is that the spectrum acquired by each detector is equivalent to a single point spectrum; therefore pre-processing, chemometrics and pattern recognition techniques are utilized with the similar goal to separate chemical and physical effects and perform a qualitative or quantitative characterization of individual sample components. In the spatial dimension, each chemical image is equivalent to a digital image and standard image analysis and robust statistical analysis can be used for feature extraction.

See also

- Multispectral image
- Microspectroscopy
- Imaging spectroscopy

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External links

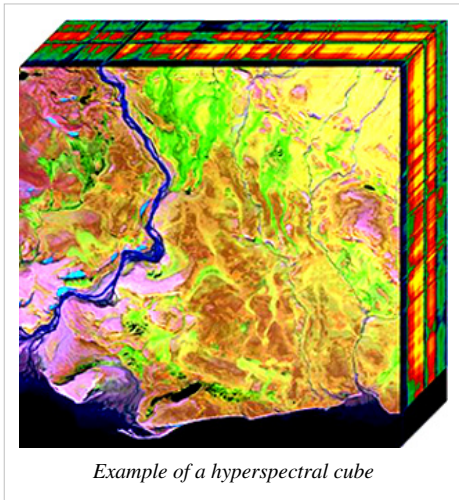
- NIR Chemical Imaging in Pharmaceutical Industry (http://www.spectroscopyeurope.com/NIR_14_3.pdf)
- Pharmaceutical Process Analytical Technology: (<http://www.fda.gov/cder/OPS/PAT.htm>)
- NIR Chemical Imaging for Counterfeit Pharmaceutical Product Analysis (<http://www.spectroscopymag.com/spectroscopy/Near-IR+Spectroscopy/NIR-Chemical-Imaging-for-Counterfeit-Pharmaceutica/ArticleStandard/Article/detail/406629>)
- Chemical Imaging: Potential New Crime Busting Tool (<http://www.sciencedaily.com/releases/2007/08/070802103435.htm>)
- Applications of Chemical Imaging in Research (<http://www3.imperial.ac.uk/vibrationalspectroscopyandchemicalimaging/research>)

Hyperspectral imaging

Hyperspectral imaging collects and processes information from across the electromagnetic spectrum. Unlike the human eye, which just sees visible light, hyperspectral imaging is more like the eyes of the mantis shrimp, which can see visible light as well as from the ultraviolet to infrared. Hyperspectral capabilities enable the mantis shrimp to recognize different types of coral, prey, or predators, all of which may appear as the same color to the human eye.

Humans build sensors and processing systems to provide the same type of capability for application in agriculture, mineralogy, physics, and surveillance. Hyperspectral sensors look at objects using a vast portion of the electromagnetic spectrum. Certain objects leave unique 'fingerprints' across the electromagnetic spectrum. These 'fingerprints' are known as spectral signatures and enable identification of the materials that make up a scanned object. For example, having the spectral signature for oil helps mineralogists find new oil fields.

Acquisition and Analysis



Example of a hyperspectral cube

Hyperspectral sensors collect information as a set of 'images'. Each image represents a range of the electromagnetic spectrum and is also known as a spectral band. These 'images' are then combined and form a three dimensional hyperspectral cube for processing and analysis.

Hyperspectral cubes are generated from airborne sensors like the NASA's *Airborne Visible/Infrared Imaging Spectrometer* (AVIRIS), or from satellites like NASA's Hyperion.^[1] However, for many development and validation studies handheld sensors are used.^[2]

The precision of these sensors is typically measured in spectral resolution, which is the width of each band of the spectrum that is captured. If the scanner picks up on a large number of fairly narrow frequency bands, it is possible to identify objects even if said objects are only captured in a handful of pixels. However, spatial resolution is

a factor in addition to spectral resolution. If the pixels are too large, then multiple objects are captured in the same pixel and become difficult to identify. If the pixels are too small, then the energy captured by each sensor-cell is low, and the decreased signal-to-noise ratio reduces the reliability of measured features.

MicroMSI, Opticks and Envi are three remote sensing applications that support the processing and analysis of hyperspectral data. The acquisition and processing of hyperspectral images is also referred to as imaging spectroscopy.

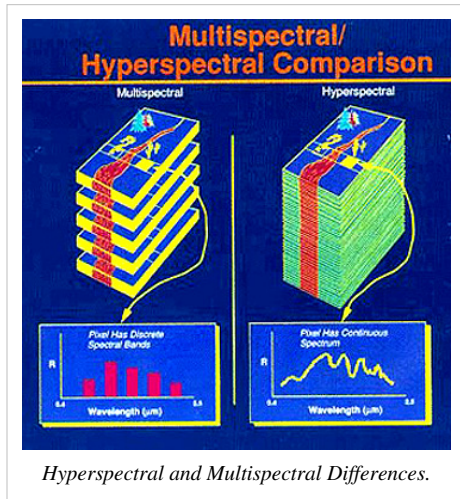
Differences between hyperspectral and multispectral imaging

Hyperspectral imaging is part of a class of techniques commonly referred to as spectral imaging or spectral analysis. Hyperspectral imaging is related to multispectral imaging. The distinction between hyper- and multi-spectral should not be based on a random or arbitrary "number of bands". A distinction that is based on the type of measurement may be more appropriate.

Multispectral deals with several images at discrete and somewhat narrow bands. The "discrete and somewhat narrow" is what distinguishes multispectral in the visible from color photography. A multispectral sensor may have many bands covering the spectrum from the visible to the longwave infrared. Multispectral images do not produce the "spectrum" of an object. Landsat is an excellent example.

Hyperspectral deals with imaging narrow spectral bands over a contiguous spectral range, and produce the spectra of all pixels in the scene. So a sensor with only 20 bands can also be hyperspectral when it covers the range from 500 to 700 nm with 20 10-nm wide bands. (While a sensor with 20 discrete bands covering the VIS, NIR, SWIR, MWIR, and LWIR would be considered multispectral.)

Ultraspectral could be reserved for interferometer type imaging sensors with a very fine spectral resolution. These sensor often have (but not necessarily) a low spatial resolution of several pixels only, a restriction imposed by the high data rate.



Hyperspectral and Multispectral Differences.

Applications

Hyperspectral remote sensing is used in a wide array of real-life applications. Although originally developed for mining and geology (the ability of hyperspectral imaging to identify various minerals makes it ideal for the mining and oil industries, where it can be used to look for ore and oil^{[2] [3]}) it has now spread into fields as widespread as ecology and surveillance, as well as historical manuscript research such as the imaging of the Archimedes Palimpsest. This technology is continually becoming more available to the public, and has been used in a wide variety of ways. Organizations such as NASA and the USGS have catalogues of various minerals and their spectral signatures, and have posted them online to make them readily available for researchers.

Agriculture

Although the costs of acquiring hyperspectral images is typically high, for specific crops and in specific climates hyperspectral remote sensing is used more and more for monitoring the development and health of crops. In Australia work is under way to use imaging spectrometers to detect grape variety, and develop an early warning system for disease outbreaks.^[4] Furthermore work is underway to use hyperspectral data to detect the chemical composition of plants^[5] which can be used to detect the nutrient and water status of wheat in irrigated systems^[6].

Another important area in agriculture is the detection of animal proteins in compound feeds in order to avoid the Bovine spongiform encephalopathy (BSE) or mad-cow disease (MCD). For this, different studies have been done in order to propose alternative tools to the reference method (classical microscopy). One of the first alternatives is the use of NIR microscopy (Infrared microscopy), which combines the advantages of microscopy and NIR. In 2004, the first study relating this problematic with Hyperspectral imaging was published^[7]. Hyperspectral libraries are constructed, which are representative of the wide diversity of ingredients usually present in the preparation of compound feeds. These libraries can be used together with chemometric tools to investigate the limit of detection, specificity and reproducibility of the NIR hyperspectral imaging method for the detection and quantification of animal ingredient in feed.

Mineralogy

The original field of development for hyperspectral remote sensing, hyperspectral sensing of minerals is now well developed. Many minerals can be identified from images, and their relation to the presence of valuable minerals such as gold and diamonds is well understood. Currently the move is towards understanding the relation between oil and gas leakages from pipelines and natural wells; their effect on the vegetation and the spectral signatures. Recent work includes the PhD dissertations of Werff^[8] and Noomen^[9].

Physics

Physicists use an electron microscopy technique that involves microanalysis using either Energy dispersive X-ray spectroscopy (EDS), Electron energy loss spectroscopy (EELS), Infrared Spectroscopy (IR), Raman Spectroscopy, or cathodoluminescence (CL) spectroscopy, in which the entire spectrum measured at each point is recorded. EELS hyperspectral imaging is performed in a scanning transmission electron microscope (STEM); EDS and CL mapping can be performed in STEM as well, or in a scanning electron microscope or electron probe microanalyzer (EPMA). Often, multiple techniques (EDS, EELS, CL) are used simultaneously.

In a "normal" mapping experiment, an image of the sample will be made that is simply the intensity of a particular emission mapped in an XY raster. For example, an EDS map could be made of a steel sample, in which iron x-ray intensity is used for the intensity grayscale of the image. Dark areas in the image would indicate not-iron-bearing impurities. This could potentially give misleading results; if the steel contained tungsten inclusions, for example, the high atomic number of tungsten could result in bremsstrahlung radiation that made the iron-free areas *appear* to be rich in iron.

By hyperspectral mapping, instead, the entire spectrum at each mapping point is acquired, and a quantitative analysis can be performed by computer post-processing of the data, and a quantitative map of iron content produced. This would show which areas contained no iron, despite the anomalous x-ray counts caused by bremsstrahlung. Because EELS core-loss edges are small signals on top of a large background, hyperspectral imaging allows large improvements to the quality of EELS chemical maps.

Similarly, in CL mapping, small shifts in the peak emission energy could be mapped, which would give information regarding slight chemical composition changes or changes in the stress state of a sample.

Surveillance

Hyperspectral surveillance is the implementation of hyperspectral scanning technology for surveillance purposes. Hyperspectral imaging is particularly useful in military surveillance because of measures that military entities now take to avoid airborne surveillance. Airborne surveillance has been in effect since soldiers used tethered balloons to spy on troops during the American Civil War, and since that time we have learned not only to hide from the naked eye, but to mask our heat signature to blend in to the surroundings and avoid infrared scanning, as well. The idea that drives hyperspectral surveillance is that hyperspectral scanning draws information from such a large portion of the light spectrum that any given object should have a unique spectral signature in at least a few of the many bands that get scanned.^[1]

Advantages and disadvantages

The primary advantages to hyperspectral imaging is that, because an entire spectrum is acquired at each point, the operator needs no prior knowledge of the sample, and post-processing allows all available information from the dataset to be mined.

The primary disadvantages are cost and complexity. Fast computers, sensitive detectors, and large data storage capacities are needed for analyzing hyperspectral data. Significant data storage capacity is necessary since hyperspectral cubes are large multi-dimensional datasets, potentially exceeding hundreds of megabytes. All of these factors greatly increase the cost of acquiring and processing hyperspectral data. Also, one of the hurdles that researchers have had to face is finding ways to program hyperspectral satellites to sort through data on their own and transmit only the most important images, as both transmission and storage of that much data could prove difficult and costly.^[1] As a relatively new analytical technique, the full potential of hyperspectral imaging has not yet been realized.

See also

- Airborne Real-time Cueing Hyperspectral Enhanced Reconnaissance
 - Full Spectral Imaging
 - Multi-spectral image
 - Chemical imaging
 - Remote Sensing
 - Sensor fusion
 - ERDAS IMAGINE
 - Liquid Crystal Tunable Filter
-

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External links

- SpecTIR (<http://www.spectir.com/>) - Hyperspectral solutions and end to end global data collection & analysis
- Opticks (<http://opticks.org/>) - open source, remote sensing application and development framework.
- ITT Visual Information Solutions - ENVI Hyperspectral Image Processing Software (<http://www.ittvis.com/ProductServices/ENVI.aspx>)
- A Hyperspectral Imaging Prototype (http://www.inrim.it/res/hyperspectral_imaging/) Fourier transform spectroscopy is combined with Fabry-Perot interferometry
- Middleton Research (<http://www.middletonresearch.com>) Hyperspectral Imaging products, custom engineering solutions
- Photon etc. (<http://photonetc.com/index.php?lan=en&sec=300&sub1=3000&sub2=1023>) Hyperspectral Imaging Systems
- UmBio - Evince. Hyperspectral image analysis in real-time. Visual information solutions, see industrial demo movies (http://beta.umbio.com/Public_files/Products/Evince_Image/EvinceImage.aspx)
- A Matlab Hyperspectral Toolbox (<http://matlabhyperspec.sourceforge.net/>)
- Telops Hyper-Cam (<http://www.hyper-cam.com/>) Commercial infrared hyperspectral camera

Multi-spectral image

A **Multi-spectral image** is one that captures image data at specific frequencies across the electromagnetic spectrum. The wavelengths may be separated by filters or by the use of instruments that are sensitive to particular wavelengths, including light from frequencies beyond the visible light range, such as infrared. Multi-spectral imaging can allow extraction of additional information that the human eye fails to capture with its receptors for red, green and blue. It was originally developed for space-based imaging.

Multi-spectral images are the main type of images acquired by Remote sensing (RS) radiometers. Dividing the spectrum into many bands, multi-spectral is the opposite of panchromatic which records only the total intensity of radiation falling on each pixel. Usually satellites have 3 to 7 or more radiometers (Landsat has 7). Each one acquires one digital image (in remote sensing, called a *scene*) in a small band of visible spectra, ranging 0.7 μm to 0.4 μm , called red-green-blue (RGB) region, and going to infra-red wavelengths of 0.7 μm to 10 or more μm , classified as NIR-Near InfraRed, MIR-Middle InfraRed and FIR-Far InfraRed or Thermal. In the Landsat case the 7 scenes comprise a 7 band multi spectral image. Multispectral images with more numerous bands or finer spectral resolution or wider spectral coverage may be called "hyperspectral" or "ultra-spectral".

This technology has also assisted in the interpretation of ancient papyri such as those found at Herculaneum, by imaging the fragments in the infrared range (1000nm). Often the text on the documents appears to be as black ink on black paper to the naked eye. At 1000nm, the difference in light reflectivity makes the text clearly readable. It has also been used to image the Archimedes Palimpsest by imaging the parchment leaves in bandwidths from 365-870 nm and then using advanced digital image processing techniques to reveal the under text of Archimedes work.

The availability of wavelengths for remote sensing and imaging is limited by infrared window and optical window.

Spectral bands

The wavelengths are approximate; exact values depend on the particular satellite's instruments:

- **Blue**, 450-515..520 nm, used for atmospheric and deep water imaging. Can reach within 150 feet (46 m) deep in clear water.
 - **Green**, 515..520-590..600 nm, used for imaging of vegetation and deep water structures, up to 90 feet (27 m) in clear water.
 - **Red**, 600..630-680..690 nm, used for imaging of man-made objects, water up to 30 feet (9.1 m) deep, soil, and vegetation.
 - **Near infrared**, 750-900 nm, primarily for imaging of vegetation.
 - **Mid-infrared**, 1550-1750 nm, for imaging vegetation and soil moisture content, and some forest fires.
 - **Mid-infrared**, 2080-2350 nm, for imaging soil, moisture, geological features, silicates, clays, and fires.
 - **Thermal infrared**, 10400-12500 nm, uses emitted radiation instead of reflected, for imaging of geological structures, thermal differences in water currents, fires, and for night studies.
 - **Radar** and related technologies, useful for mapping terrain and for detecting various objects.
-

Spectral band usage

For different purposes, different combinations of spectral bands can be used. They are usually represented with red, green, and blue channels. Mapping of bands to colors depends on the purpose of the image and the personal preferences of the analysts. Thermal infrared is often omitted from consideration due to poor spatial resolution, except for special purposes.

- **True-color.** Uses only red, green, and blue channels, mapped to their respective colors. A plain color photograph. Good for analyzing man-made objects. Easy to understand for beginner analysts.
- **Green-red-infrared,** where blue channel is replaced with near infrared. Vegetation, highly reflective in near IR, then shows as blue. This combination is often used for detection of vegetation and camouflage.
- **Blue-nearIR-midIR,** where blue channel uses visible blue, green uses near-infrared (so vegetation stays green), and mid-infrared is shown as red. Such images allow seeing the water depth, vegetation coverage, soil moisture content, and presence of fires, all in a single image.

Many other combinations are in use. Near infrared is often shown as red, making vegetation covered areas appear red.

Multispectral Data Analysis Software

- MicroMSI endorsed by the NGA.
- Opticks - an open source remote sensing application.

See also

- Hyperspectral imaging
- Full Spectral Imaging
- Remote sensing
- Spy satellite
- Imaging spectroscopy
- Imaging spectrometer
- Liquid Crystal Tunable Filter
- Satellite imagery

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Fluorescence Imaging

A **fluorescence microscope** (colloquially synonymous with *epifluorescence microscope*) is an optical microscope used to study properties of organic or inorganic substances using the phenomena of fluorescence and phosphorescence instead of, or in addition to, reflection and absorption.^{[1] [2]}

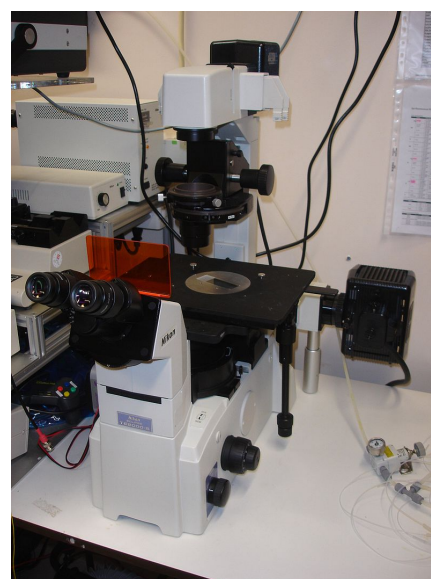


An upright fluorescence microscope (Olympus BX61) with the fluorescent filter cube turret above the objective lenses, coupled with a digital camera.

Technique

In most cases, a component of interest in the specimen can be labeled specifically with a fluorescent molecule called a fluorophore (such as green fluorescent protein (GFP), fluorescein or DyLight 488).^[1] The specimen is illuminated with light of a specific wavelength (or wavelengths) which is absorbed by the fluorophores, causing them to emit light of longer wavelengths (i.e. of a different color than the absorbed light). The illumination light is separated from the much weaker emitted fluorescence through the use of a spectral emission filter. Typical components of a fluorescence microscope are the light source (xenon arc lamp or mercury-vapor lamp), the excitation filter, the dichroic mirror (or dichromatic beamsplitter), and the emission filter (see figure below). The filters and the dichroic are chosen to match the spectral excitation and emission characteristics of the fluorophore used to label the specimen.^[1] In this manner, the distribution of a single fluorophore (color) is imaged at a time. Multi-color images of several types of fluorophores must be composed by combining several single-color images.^[1]

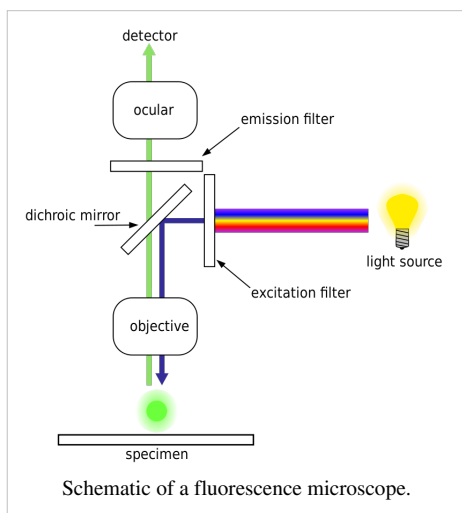
Most fluorescence microscopes in use are epifluorescence microscopes (i.e. excitation and observation of the fluorescence are from above (*epi*–) the specimen). These microscopes have become an important part in the field of biology, opening the doors for more advanced microscope designs, such as the confocal microscope and the total internal reflection fluorescence microscope (TIRF).



An inverted fluorescence microscope (Nikon TE2000) with the fluorescent filter cube turret below the stage. Note the orange plate that allows the user to look at a sample while protecting their eyes from the UV light.

Fluorophores lose their ability to fluoresce as they are illuminated in a process called photobleaching. Special care must be taken to prevent photobleaching through the use of more robust fluorophores, by minimizing illumination, or by introducing a scavenger system to reduce the rate of photobleaching.

Epifluorescence microscopy



Epifluorescence microscopy is a method of fluorescence microscopy that is widely used in life sciences. The excitatory light is passed from above (or, for inverted microscopes, from below), through the objective lens and then onto the specimen instead of passing it first through the specimen. The fluorescence in the specimen gives rise to emitted light which is focused to the detector by the same objective that is used for the excitation. Since most of the excitatory light is transmitted through the specimen, only reflected excitatory light reaches the objective together with the emitted light and this method therefore gives an improved signal to noise ratio. An additional filter between the objective and the detector can filter out the remaining excitation light from fluorescent light. A common use in biology is to apply fluorescent or fluorochrome stains to the specimen in order to image distributions of proteins or other molecules of interest.

Improvements and sub-diffraction techniques

The nature of light limits the size of the spot to which light can be focused. According to the diffraction limit a focused light distribution cannot be made smaller than approximately half of the wavelength of the used light. Uncovered in the 19th century by Ernst Abbe this has been a barrier of the achievable resolution of fluorescence light microscopes for a long time. While resolution is denoted by the ability to discern different objects of the same kind, localizing or tracking of single particles have been performed with a precision much below the diffraction limit.

Several improvements in microscopy techniques have been invented in the 20th century and have resulted in increased resolution and contrast to some extent. However they did not overcome the diffraction limit. In 1978 first theoretical ideas have been developed to break this barrier by using a 4Pi microscope as a confocal laser scanning fluorescence microscope where the light is focused ideally from all sides to a common focus which is used to scan the object by 'point-by-point' excitation combined with 'point-by-point' detection^[3]. However, the first experimental demonstration of the 4pi microscope took place in 1994^[4]. The 4Pi microscopy is maximizing the amount of available focusing directions by using two opposing objective lenses or Multi-photon microscopy using redshifted light and multi-photon excitation.

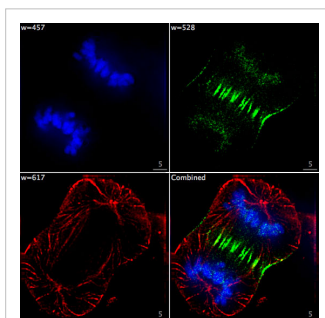
The first technique to really achieve a sub-diffraction resolution was STED microscopy, proposed in 1994. This method and all techniques following the RESOLFT concept rely on a strong non-linear interaction between light and fluorescing molecules. The molecules are driven strongly between distinguishable molecular states at each specific location, so that finally light can be emitted at only a small fraction of space, hence an increased resolution.

As well in the 1990ies another super resolution microscopy method based on wide field microscopy has been developed. Substantially improved size resolution of cellular nanostructures stained with a fluorescent marker was achieved by development of SPDM localization microscopy and the structured laser illumination (spatially modulated illumination, SMI)^[5]. Combining the principle of SPDM with SMI resulted in the development of the Vertico SMI microscope^{[6] [7]}. Single molecule detection of normal blinking fluorescent dyes like GFP can be achieved by using a further development of SPDM the so-called SPDMphymod technology which makes it possible

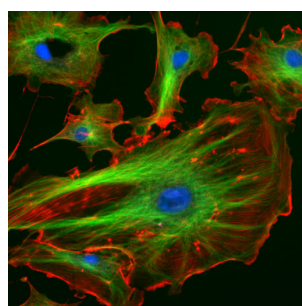
to detect and count two different fluorescent molecule types at the molecular level (this technology is referred to as 2CLM, 2 Color Localization Microscopy) ^[8].

Alternatively, the advent of photoactivated localization microscopy could achieve similar results by relying on blinking or switching of single molecules, where the fraction of fluorescing molecules is very small at each time. This stochastic response of molecules on the applied light corresponds also to a highly nonlinear interaction, leading to subdiffraction resolution.

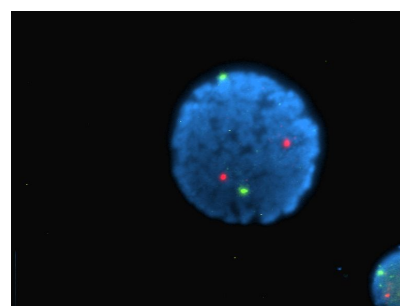
Gallery



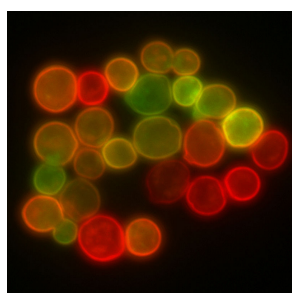
Epifluorescent imaging of the three components in a dividing human cancer cell. DNA is stained blue, a protein called INCENP is green, and the microtubules are red. Each fluorophore is imaged separately using a different combination of excitation and emission filters, and the images are captured sequentially using a digital CCD camera, then overlaid to give a complete image.



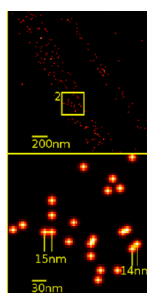
Endothelial cells under the microscope. Nuclei are stained blue with DAPI, microtubules are marked green by an antibody bound to FITC and actin filaments are labeled red with phalloidin bound to TRITC. Bovine pulmonary artery endothelial (BPAE) cells



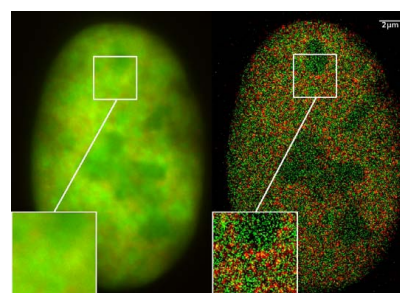
Human lymphocyte nucleus stained with DAPI with chromosome 13 (green) and 21 (red) centromere probes hybridized (Fluorescent in situ hybridization (FISH))



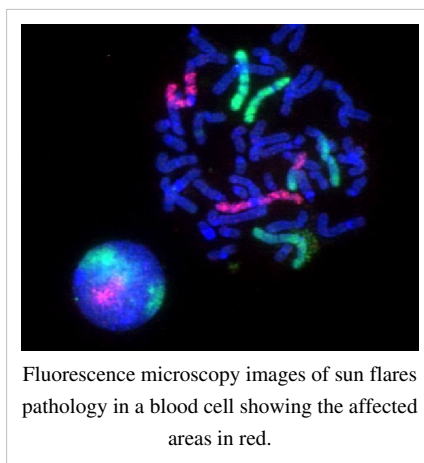
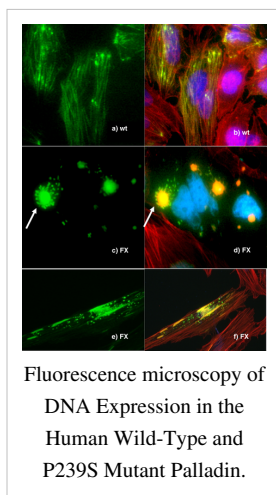
Yeast cell membrane visualized by some membrane proteins fused with RFP and GFP fluorescent markers. Imposition of light from both of markers results in yellow color.



Super Resolution Microscopy: Single YFP molecule detection in a human cancer cell. Typical distance measurements in the 15 nm range (5 nm standard deviation) measured with a Vertico-SMI/SPDMphymod microscope



Super Resolution Microscopy: Co-localization microscopy (2CLM) with GFP and RFP fusion proteins (nucleus of a bone cancer cell) 120.000 localized molecules in a wide-field area ($470 \mu\text{m}^2$) measured with a Vertico-SMI/SPDMphymod microscope



See also

- Microscope
- Mercury-vapor lamp, Xenon arc lamp
- Stokes shift

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External links

- Fluorophores.org (<http://www.fluorophores.org>) - Database of fluorescent dyes.

Fluorescence correlation spectroscopy

Fluorescence correlation spectroscopy (FCS) is a correlation analysis of fluctuation of the fluorescence intensity. The analysis provides parameters of the physics under the fluctuations. One of the interesting applications of this is an analysis of the concentration fluctuations of fluorescent particles (molecules) in solution. In this application, the fluorescence emitted from a very tiny space in solution containing a small number of fluorescent particles (molecules) is observed. The fluorescence intensity is fluctuating due to Brownian motion of the particles. In other words, the number of the particles in the sub-space defined by the optical system is randomly changing around the average number. The analysis gives the average number of fluorescent particles and average diffusion time, when the particle is passing through the space. Eventually, both the concentration and size of the particle (molecule) are determined. Since the method is observing a small number of molecule in a very tiny spot, it is a very sensitive analytical tool. Both parameters are very important and essential in the biochemical research, biophysics and chemistry. In contrast to the other method, such as HPLC analysis, this method has no physical separation process and has a good spatial resolution determined by the optics. These are of great advantage. Moreover, the method enables us to observe fluorescence-tagged molecules in the biochemical pathway in the intact living cells. Then, it opens a new area, "in situ or in vivo biochemistry", tracing biochemical pathway in the intact cells and organs.

Commonly, FCS is employed in the context of optical microscopy, in particular confocal or two-photon microscopy. In these techniques light is focused on a sample and the measured fluorescence intensity fluctuations (due to diffusion, physical or chemical reactions, aggregation, etc.) are analyzed using the temporal autocorrelation. Because the measured property is essentially related to the magnitude and/or the amount of fluctuations, there is an optimum measurement regime at the level when individual species enter or exit the observation volume (or turn on and off in the volume). When too many entities are measured at the same time the overall fluctuations are small in comparison to the total signal and may not be resolvable – in the other direction, if the individual fluctuation-events are too sparse in time, one measurement may take prohibitively too long. FCS is in a way the fluorescent counterpart to dynamic light scattering, which uses coherent light scattering, instead of (incoherent) fluorescence.

When an appropriate model is known, FCS can be used to obtain quantitative information such as

- diffusion coefficients
- hydrodynamic radii
- average concentrations
- kinetic chemical reaction rates
- singlet-triplet dynamics

Because fluorescent markers come in a variety of colors and can be specifically bound to a particular molecule (e.g. proteins, polymers, metal-complexes, etc.), it is possible to study the behavior of individual molecules (in rapid succession in composite solutions). With the development of sensitive detectors such as avalanche photodiodes the detection of the fluorescence signal coming from individual molecules in highly dilute samples has become practical. With this emerged the possibility to conduct FCS experiments in a wide variety of specimens, ranging from materials science to biology. The advent of engineered cells with genetically tagged proteins (like green fluorescent protein) has made FCS a common tool for studying molecular dynamics in living cells.

History

Signal-correlation techniques were first experimentally applied to fluorescence in 1972 by Magde, Elson, and Webb^[1], who are therefore commonly credited as the "inventors" of FCS. The technique was further developed in a group of papers by these and other authors soon after, establishing the theoretical foundations and types of applications.^{[2] [3] [4]} See Thompson (1991)^[5] for a review of that period.

Beginning in 1993^[6], a number of improvements in the measurement techniques—notably using confocal microscopy, and then two-photon microscopy—to better define the measurement volume and reject background—greatly improved the signal-to-noise ratio and allowed single molecule sensitivity.^{[7] [8]} Since then, there has been a renewed interest in FCS, and as of August 2007 there have been over 3,000 papers using FCS found in Web of Science. See Krichevsky and Bonnet^[9] for a recent review. In addition, there has been a flurry of activity extending FCS in various ways, for instance to laser scanning and spinning-disk confocal microscopy (from a stationary, single point measurement), in using cross-correlation (FCCS) between two fluorescent channels instead of autocorrelation, and in using Förster Resonance Energy Transfer (FRET) instead of fluorescence.

Typical FCS setup

The typical FCS setup consists of a laser line (wavelengths ranging typically from 405–633 nm (cw), and from 690–1100 nm (pulsed)), which is reflected into a microscope objective by a dichroic mirror. The laser beam is focused in the sample, which contains fluorescent particles (molecules) in such high dilution, that only a few are within the focal spot (usually 1–100 molecules in one fL). When the particles cross the focal volume, they fluoresce. This light is collected by the same objective and, because it is red-shifted with respect to the excitation light it passes the dichroic mirror reaching a detector, typically a photomultiplier tube or avalanche photodiode detector. The resulting electronic signal can be stored either directly as an intensity versus time trace to be analyzed at a later point, or computed to generate the autocorrelation directly (which requires special acquisition cards). The FCS curve by itself only represents a time-spectrum. Conclusions on physical phenomena have to be extracted from there with appropriate models. The parameters of interest are found after fitting the autocorrelation curve to modeled functional forms.^[10]

The measurement volume

The measurement volume is a convolution of illumination (excitation) and detection geometries, which result from the optical elements involved. The resulting volume is described mathematically by the point spread function (or PSF), it is essentially the image of a point source. The PSF is often described as an ellipsoid (with unsharp boundaries) of few hundred nanometers in focus diameter, and almost one micrometre along the optical axis. The shape varies significantly (and has a large impact on the resulting FCS curves) depending on the quality of the optical elements (it is crucial to avoid astigmatism and to check the real shape of the PSF on the instrument). In the case of confocal microscopy, and for small pinholes (around one Airy unit), the PSF is well approximated by Gaussians:

$$PSF(r, z) = I_0 e^{-2r^2/\omega_{xy}^2} e^{-2z^2/\omega_z^2}$$

where I_0 is the peak intensity, r and z are radial and axial position, and ω_{xy} and ω_z are the radial and axial radii, and $\omega_z > \omega_{xy}$. This Gaussian form is assumed in deriving the functional form of the autocorrelation.

Typically ω_{xy} is 200–300 nm, and ω_z is 2–6 times larger.^[11] One common way of calibrating the measurement volume parameters is to perform FCS on a species with known diffusion coefficient and concentration (see below). Diffusion coefficients for common fluorophores in water are given in a later section.

The Gaussian approximation works to varying degrees depending on the optical details, and corrections can sometimes be applied to offset the errors in approximation.^[12]

Autocorrelation function

The (temporal) autocorrelation function is the correlation of a time series with itself shifted by time τ , as a function of τ :

$$G(\tau) = \frac{\langle \delta I(t) \delta I(t + \tau) \rangle}{\langle I(t) \rangle^2} = \frac{\langle I(t) I(t + \tau) \rangle}{\langle I(t) \rangle^2} - 1$$

where $\delta I(t) = I(t) - \langle I(t) \rangle$ is the deviation from the mean intensity. The normalization (denominator) here is the most commonly used for FCS, because then the correlation at $\tau = 0$, $G(0)$, is related to the average number of particles in the measurement volume.

Interpreting the autocorrelation function

To extract quantities of interest, the autocorrelation data can be fitted, typically using a nonlinear least squares algorithm. The fit's functional form depends on the type of dynamics (and the optical geometry in question).

Normal diffusion

The fluorescent particles used in FCS are small and thus experience thermal motions in solution. The simplest FCS experiment is thus normal 3D diffusion, for which the autocorrelation is:

$$G(\tau) = G(0) \frac{1}{(1 + (\tau/\tau_D))(1 + a^{-2}(\tau/\tau_D))^{1/2}} + G(\infty)$$

where $a = \omega_z/\omega_{xy}$ is the ratio of axial to radial e^{-2} radii of the measurement volume, and τ_D is the characteristic residence time. This form was derived assuming a Gaussian measurement volume. Typically, the fit would have three free parameters— $G(0)$, $G(\infty)$, and τ_D —from which the diffusion coefficient and fluorophore concentration can be obtained.

With the normalization used in the previous section, $G(0)$ gives the mean number of diffusers in the volume $\langle N \rangle$, or equivalently—with knowledge of the observation volume size—the mean concentration:

$$G(0) = \frac{1}{\langle N \rangle} = \frac{1}{V_{\text{eff}} \langle C \rangle},$$

where the effective volume is found from integrating the Gaussian form of the measurement volume and is given by:

$$V_{\text{eff}} = \pi^{3/2} \omega_{xy}^2 \omega_z.$$

τ_D gives the diffusion coefficient:

$$D = \omega_{xy}^2 / 4\tau_D.$$

Anomalous diffusion

If the diffusing particles are hindered by obstacles or pushed by a force (molecular motors, flow, etc.) the dynamics is often not sufficiently well-described by the normal diffusion model, where the mean squared displacement (MSD) grows linearly with time. Instead the diffusion may be better described as anomalous diffusion, where the temporal dependence of the MSD is non-linear as in the power-law:

$$MSD = 6D_a t^\alpha$$

where D_a is an anomalous diffusion coefficient. "Anomalous diffusion" commonly refers only to this very generic model, and not the many other possibilities that might be described as anomalous. Also, a power law is, in a strict sense, the expected form only for a narrow range of rigorously defined systems, for instance when the distribution of obstacles is fractal. Nonetheless a power law can be a useful approximation for a wider range of systems.

The FCS autocorrelation function for anomalous diffusion is:

$$G(\tau) = G(0) \frac{1}{(1 + (\tau/\tau_D)^\alpha)(1 + a^{-2}(\tau/\tau_D)^\alpha)^{1/2}} + G(\infty),$$

where the anomalous exponent α is the same as above, and becomes a free parameter in the fitting.

Using FCS, the anomalous exponent has been shown to be an indication of the degree of molecular crowding (it is less than one and smaller for greater degrees of crowding)^[13].

Polydisperse diffusion

If there are diffusing particles with different sizes (diffusion coefficients), it is common to fit to a function that is the sum of single component forms:

$$G(\tau) = G(0) \sum_i \frac{\alpha_i}{(1 + (\tau/\tau_{D,i})^\alpha)(1 + a^{-2}(\tau/\tau_{D,i})^\alpha)^{1/2}} + G(\infty)$$

where the sum is over the number different sizes of particle, indexed by i , and α_i gives the weighting, which is related to the quantum yield and concentration of each type. This introduces new parameters, which makes the fitting more difficult as a higher dimensional space must be searched. Nonlinear least square fitting typically becomes unstable with even a small number of $\tau_{D,i}$ s. A more robust fitting scheme, especially useful for polydisperse samples, is the Maximum Entropy Method^[14].

Diffusion with flow

With diffusion together with a uniform flow with velocity v in the lateral direction, the autocorrelation is^[15]:

where $\tau_v = \omega_{xy}/v$ is the average residence time if there is only a flow (no diffusion).

Chemical relaxation

A wide range of possible FCS experiments involve chemical reactions that continually fluctuate from equilibrium because of thermal motions (and then "relax"). In contrast to diffusion, which is also a relaxation process, the fluctuations cause changes between states of different energies. One very simple system showing chemical relaxation would be a stationary binding site in the measurement volume, where particles only produce signal when bound (e.g. by FRET, or if the diffusion time is much faster than the sampling interval). In this case the autocorrelation is:

$$G(\tau) = G(0) \exp(-\tau/\tau_B) + G(\infty)$$

where

$$\tau_B = (k_{on} + k_{off})^{-1}$$

is the relaxation time and depends on the reaction kinetics (on and off rates), and:

$$G(0) = \frac{1}{\langle N \rangle} \frac{k_{on}}{k_{off}} = \frac{1}{\langle N \rangle} K$$

is related to the equilibrium constant K .

Most systems with chemical relaxation also show measureable diffusion as well, and the autocorrelation function will depend on the details of the system. If the diffusion and chemical reaction are decoupled, the combined autocorrelation is the product of the chemical and diffusive autocorrelations.

Triplet state correction

The autocorrelations above assume that the fluctuations are not due to changes in the fluorescent properties of the particles. However, for the majority of (bio)organic fluorophores--e.g. green fluorescent protein, rhodamine, Cy3 and Alexa Fluor dyes--some fraction of illuminated particles are excited to a triplet state (or other non-radiative decaying states) and then do not emit photons for a characteristic relaxation time τ_F . Typically τ_F is on the order of microseconds, which is usually smaller than the dynamics of interest (e.g. τ_D) but large enough to be measured. A

multiplicative term is added to the autocorrelation account for the triplet state. For normal diffusion:

where F is the fraction of particles that have entered the triplet state and τ_F is the corresponding triplet state relaxation time. If the dynamics of interest are much slower than the triplet state relaxation, the short time component of the autocorrelation can simply be truncated and the triplet term is unnecessary.

Common fluorescent probes

The fluorescent species used in FCS is typically a biomolecule of interest that has been tagged with a fluorophore (using immunohistochemistry for instance), or is a naked fluorophore that is used to probe some environment of interest (e.g. the cytoskeleton of a cell). The following table gives diffusion coefficients of some common fluorophores in water at room temperature, and their excitation wavelengths.

Fluorescent dye	$D (\times 10^{-10} \text{ m}^2 \text{ s}^{-1})$	Excitation wavelength (nm)	Reference
Rhodamine 6G	2.8, 3.0, 4.14 ± 0.05 @ 25.00 °C	514	[16] , [17] , [18]
Rhodamine 110	2.7	488	[19]
Tetramethyl rhodamine	2.6	543	
Cy3	2.8	543	
Cy5	$2.5, 3.7 \pm 0.15$ @ 25.00 °C	633	[20] , [21]
carboxyfluorescein	3.2	488	
Alexa-488	$1.96, 4.35$ @ 22.5 ± 0.5 °C	488	[22] [23]
Atto655-maleimide	4.07 ± 0.1 @ 25.00 °C	663	[24]
Atto655-carboxylic acid	4.26 ± 0.08 @ 25.00 °C	663	[25]
2', 7'-difluorofluorescein (Oregon Green488)	4.11 ± 0.06 @ 25.00 °C	498	[26]

Variations of FCS

FCS almost always refers to the single point, single channel, temporal autocorrelation measurement, although the term "fluorescence correlation spectroscopy" out of its historical scientific context implies no such restriction. FCS has been extended in a number of variations by different researchers, with each extension generating another name (usually an acronym).

Fluorescence cross-correlation spectroscopy (FCCS)

FCS is sometimes used to study molecular interactions using differences in diffusion times (e.g. the product of an association reaction will be larger and thus have larger diffusion times than the reactants individually); however, FCS is relatively insensitive to molecular mass as can be seen from the following equation relating molecular mass to the diffusion time of globular particles (e.g. proteins):

$$\tau_D = \frac{3\pi\omega_{xy}^2\eta}{2kT}(M)^{1/3}$$

where η is the viscosity of the sample and M is the molecular mass of the fluorescent species. In practice, the diffusion times need to be sufficiently different--a factor of at least **1.6**--which means the molecular masses must differ by a factor of **4**.^[27] Dual color fluorescence cross-correlation spectroscopy (FCCS) measures interactions by cross-correlating two or more fluorescent channels (one channel for each reactant), which distinguishes interactions more sensitively than FCS, particularly when the mass change in the reaction is small.

Brightness analysis methods (N&B,^[28] PCH,^[29] FIDA,^[30] Cumulant Analysis^[31])

Fluorescence cross correlation spectroscopy overcomes the weak dependence of diffusion rate on molecular mass by looking at multicolor coincidence. What about homo-interactions? The solution lies in brightness analysis. These methods use the heterogeneity in the intensity distribution of fluorescence to measure the molecular brightness of different species in a sample. Since dimers will contain twice the number of fluorescent labels as monomers, their molecular brightness will be approximately double that of monomers. As a result, the relative brightness is sensitive a measure of oligomerization. The average molecular brightness ($\langle \epsilon \rangle$) is related to the variance (σ^2) and the average intensity ($\langle I \rangle$) as follows:^[32]

$$\langle \epsilon \rangle = \frac{\sigma^2 - \langle I \rangle}{\langle I \rangle} = \sum_i f_i \epsilon_i$$

Here f_i and ϵ_i are the fractional intensity and molecular brightness, respectively, of species i .

Two- and three- photon FCS excitation

Several advantages in both spatial resolution and minimizing photodamage/photobleaching in organic and/or biological samples are obtained by two-photon or three-photon excitation FCS^{[33] [34] [35] [36] [37]}.

FRET-FCS

Another FCS based approach to studying molecular interactions uses fluorescence resonance energy transfer (FRET) instead of fluorescence, and is called FRET-FCS.^[38] With FRET, there are two types of probes, as with FCCS; however, there is only one channel and light is only detected when the two probes are very close—close enough to ensure an interaction. The FRET signal is weaker than with fluorescence, but has the advantage that there is only signal during a reaction (aside from autofluorescence).

Image correlation spectroscopy (ICS)

When the motion is slow (in biology, for example, diffusion in a membrane), getting adequate statistics from a single-point FCS experiment may take a prohibitively long time. More data can be obtained by performing the experiment in multiple spatial points in parallel, using a laser scanning confocal microscope. This approach has been called Image Correlation Spectroscopy (ICS)^[39]. The measurements can then be averaged together.

Another variation of ICS performs a spatial autocorrelation on images, which gives information about the concentration of particles^[40]. The correlation is then averaged in time.

A natural extension of the temporal and spatial correlation versions is spatio-temporal ICS (STICS)^[41]. In STICS there is no explicit averaging in space or time (only the averaging inherent in correlation). In systems with non-isotropic motion (e.g. directed flow, asymmetric diffusion), STICS can extract the directional information. A variation that is closely related to STICS (by the Fourier transform) is k -space Image Correlation Spectroscopy (kICS).^[42]

There are cross-correlation versions of ICS as well.^[39]

Scanning FCS variations

Some variations of FCS are only applicable to serial scanning laser microscopes. Image Correlation Spectroscopy and its variations all were implemented on a scanning confocal or scanning two photon microscope, but transfer to other microscopes, like a spinning disk confocal microscope. Raster ICS (RICS)^[43], and position sensitive FCS (PSFCS)^[44] incorporate the time delay between parts of the image scan into the analysis. Also, low dimensional scans (e.g. a circular ring)^[45]—only possible on a scanning system—can access time scales between single point and full image measurements. Scanning path has also been made to adaptively follow particles.^[46]

Spinning disk FCS, and spatial mapping

Any of the image correlation spectroscopy methods can also be performed on a spinning disk confocal microscope, which in practice can obtain faster imaging speeds compared to a laser scanning confocal microscope. This approach has recently been applied to diffusion in a spatially varying complex environment, producing a pixel resolution map of a diffusion coefficient.^[47] The spatial mapping of diffusion with FCS has subsequently been extended to the TIRF system.^[48] Spatial mapping of dynamics using correlation techniques had been applied before, but only at sparse points^[49] or at coarse resolution^[41].

Total internal reflection FCS

Total internal reflection fluorescence (TIRF) is a microscopy approach that is only sensitive to a thin layer near the surface of a coverslip, which greatly minimizes background fluorescence. FCS has been extended to that type of microscope, and is called TIR-FCS^[50]. Because the fluorescence intensity in TIRF falls off exponentially with distance from the coverslip (instead of as a Gaussian with a confocal), the autocorrelation function is different.

Other fluorescent dynamical approaches

There are two main non-correlation alternatives to FCS that are widely used to study the dynamics of fluorescent species.

Fluorescence recovery after photobleaching (FRAP)

In FRAP, a region is briefly exposed to intense light, irreversibly photobleaching fluorophores, and the fluorescence recovery due to diffusion of nearby (non-bleached) fluorophores is imaged. A primary advantage of FRAP over FCS is the ease of interpreting qualitative experiments common in cell biology. Differences between cell lines, or regions of a cell, or before and after application of drug, can often be characterized by simple inspection of movies. FCS experiments require a level of processing and are more sensitive to potentially confounding influences like: rotational diffusion, vibrations, photobleaching, dependence on illumination and fluorescence color, inadequate statistics, etc. It is much easier to change the measurement volume in FRAP, which allows greater control. In practice, the volumes are typically larger than in FCS. While FRAP experiments are typically more qualitative, some researchers are studying FRAP quantitatively and including binding dynamics.^[51] A disadvantage of FRAP in cell biology is the free radical perturbation of the cell caused by the photobleaching. It is also less versatile, as it cannot measure concentration or rotational diffusion, or co-localization. FRAP requires a significantly higher concentration of fluorophores than FCS.

Particle tracking

In particle tracking, the trajectories of a set of particles are measured, typically by applying particle tracking algorithms to movies.^[52] Particle tracking has the advantage that all the dynamical information is maintained in the measurement, unlike FCS where correlation averages the dynamics to a single smooth curve. The advantage is apparent in systems showing complex diffusion, where directly computing the mean squared displacement allows straightforward comparison to normal or power law diffusion. To apply particle tracking, the particles have to be distinguishable and thus at lower concentration than required of FCS. Also, particle tracking is more sensitive to noise, which can sometimes affect the results unpredictably.

See also

- Confocal microscopy
- Fluorescence cross-correlation spectroscopy, FCCS
- FRET
- Dynamic light scattering
- Diffusion coefficient

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External links

- Single-molecule spectroscopic methods (<http://dx.doi.org/10.1016/j.sbi.2004.09.004>)
- FCS Classroom (<http://www.fcsxpert.com/classroom>)
- Stowers Institute FCS Tutorial (<http://research.stowers-institute.org/microscopy/external/Technology/FCS/index.htm>)
- Cell Migration Consortium FCS Tutorial (http://www.cellmigration.org/resource/imaging/imaging_approaches_correlation_microscopy.shtml)

Fluorescence cross-correlation spectroscopy

Fluorescence cross-correlation spectroscopy (FCCS) was introduced by Eigen and Rigler in 1994 and experimentally realized by Schwille in 1997. It extends the fluorescence correlation spectroscopy (FCS) procedure by introducing high sensitivity for distinguishing fluorescent particles which have a similar diffusion coefficient. FCCS uses two species which are independently labelled with two spectrally separated fluorescent probes. These fluorescent probes are excited and detected by two different laser light sources and detectors commonly known as green and red respectively. Both laser light beams are focused into the sample and tuned so that they overlap to form a superimposed confocal observation volume.

The normalized cross-correlation function is defined for two fluorescent species G and R which are independent green, G and red, R channels as follows:

where differential fluorescent signals δI_G at a specific time, t and δI_R at a delay time, τ later is correlated with each other.

Modeling

Cross-correlation curves are modeled according to a slightly more complicated mathematical function than applied in FCS. First of all, the effective superimposed observation volume in which the G and R channels form a single observation volume, $V_{eff, RG}$ in the solution:

$$V_{eff, RG} = \pi^{3/2} (\omega_{xy, G}^2 + \omega_{xy, R}^2) (\omega_{z, G}^2 + \omega_{z, R}^2)^{1/2} / 2^{3/2}$$

where $\omega_{xy, G}^2$ and $\omega_{xy, R}^2$ are radial parameters and $\omega_{z, G}$ and $\omega_{z, R}$ are the axial parameters for the G and R channels respectively.

The diffusion time, $\tau_{D, GR}$ for a doubly (G and R) fluorescent species is therefore described as follows:

$$\tau_{D, GR} = \frac{\omega_{xy, G}^2 + \omega_{xy, R}^2}{8D_{GR}}$$

where D_{GR} is the diffusion coefficient of the doubly fluorescent particle.

The cross-correlation curve generated from diffusing doubly labelled fluorescent particles can be modelled in separate channels as follows:

$$G_G(\tau) = 1 + \frac{(\langle C_G \rangle Diff_k(\tau) + \langle C_{GR} \rangle Diff_k(\tau))}{V_{eff, GR}(\langle C_G \rangle + \langle C_{GR} \rangle)^2}$$

$$G_R(\tau) = 1 + \frac{(\langle C_R \rangle \text{Diff}_k(\tau) + \langle C_{GR} \rangle \text{Diff}_k(\tau))}{V_{eff,GR}(\langle C_R \rangle + \langle C_{GR} \rangle)^2}$$

In the ideal case, the cross-correlation function is proportional to the concentration of the doubly labeled fluorescent complex:

$$\text{with } \text{Diff}_k(\tau) = \frac{1}{(1 + \frac{\tau}{\tau_{D,i}})(1 + a^{-2}(\frac{\tau}{\tau_{D,i}})^{1/2})}$$

Contrary to FCS, the intercept of the cross-correlation curve does not yield information about the doubly labelled fluorescent particles in solution.

See also

- Fluorescence correlation spectroscopy
- Dynamic light scattering
- Fluorescence spectroscopy
- Diffusion coefficient

External links

- FCS Classroom ^[1]

References

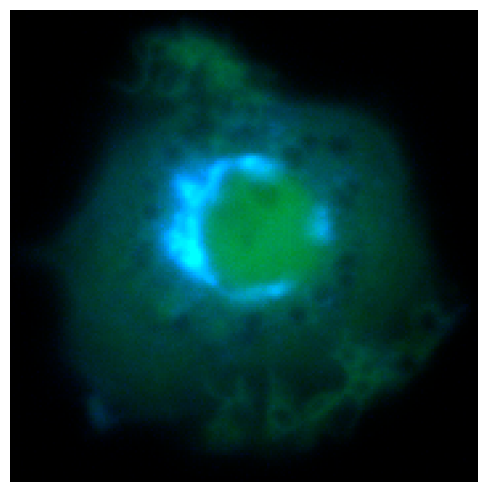
- [1] <http://www.fcsxpert.com/classroom>

Förster resonance energy transfer

Förster resonance energy transfer (abbreviated **FRET**), also known as **fluorescence resonance energy transfer**, **resonance energy transfer (RET)** or **electronic energy transfer (EET)**, is a mechanism describing energy transfer between two chromophores.

A donor chromophore, initially in its electronic excited state, may transfer energy to an acceptor chromophore (in proximity, typically less than 10 nm) through nonradiative dipole–dipole coupling. This mechanism is termed "Förster resonance energy transfer" and is named after the German scientist Theodor Förster.^[2] When both chromophores are fluorescent, the term "fluorescence resonance energy transfer" is often used instead, although the energy is not actually transferred by fluorescence.^[3]

^[4] In order to avoid an erroneous interpretation of the phenomenon that (even when occurring between two fluorescent chromophores) is always a nonradiative transfer of energy, the name "Förster resonance energy transfer" is preferred to "fluorescence resonance energy transfer" – although the latter enjoys common usage in scientific literature, despite being incorrect. FRET is analogous to near field communication, in that the radius of interaction is much smaller than the



Fluorescently-labeled guanosine 5'-triphosphate hydrolase ARF reveals the protein's localization in the Golgi apparatus of a living macrophage. FRET studies revealed ARF activation in the Golgi and in the formation of phagosomes.^[1]

wavelength of light emitted. In the near field region, the excited chromophore emits a virtual photon that is instantly absorbed by a receiving chromophore. These virtual photons are undetectable, since their existence violates the conservation of energy and momentum, and hence FRET is known as a *radiationless* mechanism. From quantum electrodynamical calculations, it is determined that radiationless (FRET) and radiative energy transfer are the short- and long-range asymptotes of a single unified mechanism.^{[5] ,[6]}

Theoretical basis

The FRET efficiency (E) is the quantum yield of the energy transfer transition, *i.e.* the fraction of energy transfer event occurring per donor excitation event:

$$E = \frac{k_{ET}}{k_f + k_{ET} + \sum k_i}$$

where k_{ET} is the rate of energy transfer, k_f the radiative decay rate and the k_i are the rate constants of any other de-excitation pathway.

The FRET efficiency depends on many parameters that can be grouped as follows:

- The distance between the donor and the acceptor
- The spectral overlap of the donor emission spectrum and the acceptor absorption spectrum.
- The relative orientation of the donor emission dipole moment and the acceptor absorption dipole moment.

E depends on the donor-to-acceptor separation distance r with an inverse 6th power law due to the dipole-dipole coupling mechanism:

$$E = \frac{1}{1 + (r/R_0)^6}$$

with R_0 being the Förster distance of this pair of donor and acceptor, *i.e.* the distance at which the energy transfer efficiency is 50%. The Förster distance depends on the overlap integral of the donor emission spectrum with the acceptor absorption spectrum and their mutual molecular orientation as expressed by the following equation:

$$R_0^6 = \frac{9 Q_0 (\ln 10) \kappa^2 J}{128 \pi^5 n^4 N_A}$$

where Q_0 is the fluorescence quantum yield of the donor in the absence of the acceptor, κ^2 is the dipole orientation factor, n is the refractive index of the medium, N_A is Avogadro's number, and J is the spectral overlap integral calculated as

$$J = \int f_D(\lambda) \epsilon_A(\lambda) \lambda^4 d\lambda$$

where f_D is the normalized donor emission spectrum, and ϵ_A is the acceptor molar extinction coefficient. $\kappa^2 = 2/3$ is often assumed. This value is obtained when both dyes are freely rotating and can be considered to be isotropically oriented during the excited state lifetime. If either dye is fixed or not free to rotate, then $\kappa^2 = 2/3$ will not be a valid assumption. In most cases, however, even modest reorientation of the dyes results in enough orientational averaging that $\kappa^2 = 2/3$ does not result in a large error in the estimated energy transfer distance due to the sixth power dependence of R_0 on κ^2 . Even when κ^2 is quite different from $2/3$ the error can be associated with a shift in R_0 and thus determinations of changes in relative distance for a particular system are still valid. Fluorescent proteins do not reorient on a timescale that is faster than their fluorescence lifetime. In this case $0 \leq \kappa^2 \leq 4$.

The FRET efficiency relates to the quantum yield and the fluorescence lifetime of the donor molecule as follows:

$$E = 1 - \tau'_D / \tau_D$$

where τ'_D and τ_D are the donor fluorescence lifetimes in the presence and absence of an acceptor, respectively, or as

$$E = 1 - F'_D / F_D$$

where F'_D and F_D are the donor fluorescence intensities with and without an acceptor, respectively.

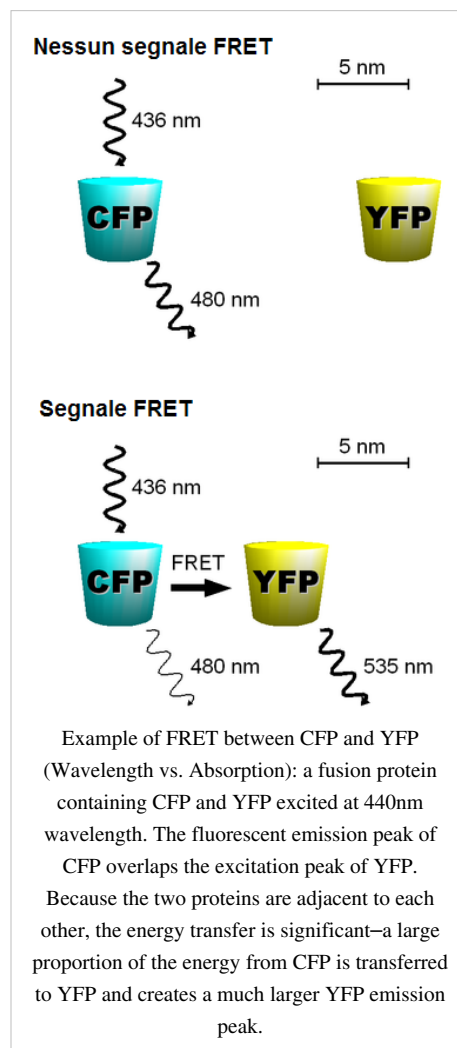
Methods

In fluorescence microscopy, fluorescence confocal laser scanning microscopy, as well as in molecular biology, FRET is a useful tool to quantify molecular dynamics in biophysics and biochemistry, such as protein-protein interactions, protein-DNA interactions, and protein conformational changes. For monitoring the complex formation between two molecules, one of them is labeled with a donor and the other with an acceptor, and these fluorophore-labeled molecules are mixed. When they are dissociated, the donor emission is detected upon the donor excitation. On the other hand, when the donor and acceptor are in proximity (1-10 nm) due to the interaction of the two molecules, the acceptor emission is predominantly observed because of the intermolecular FRET from the donor to the acceptor. For monitoring protein conformational changes, the target protein is labeled with a donor and an acceptor at two loci. When a twist or bend of the protein brings the change in the distance or relative orientation of the donor and acceptor, FRET change is observed. If a molecular interaction or a protein conformational change is dependent on ligand binding, this FRET technique is applicable to fluorescent indicators for the ligand detection.

FRET studies are scalable: the extent of energy transfer is often quantified from the milliliter scale of cuvette-based experiments to the femtoliter scale of microscopy-based experiments. This quantification can be based directly (sensitized emission method) on detecting two emission channels under two different excitation conditions (primarily donor and primarily acceptor). However, for robustness reasons, FRET quantification is most often based on measuring changes in fluorescence intensity or fluorescence lifetime upon changing the experimental conditions (e.g. a microscope image of donor emission is taken with the acceptor being present. The acceptor is then bleached, such that it is incapable of accepting energy transfer and another donor emission image is acquired. A pixel-based quantification using the second equation in the theory section above is then possible.) An alternative way of temporarily deactivating the acceptor is based on its fluorescence saturation. Exploiting polarisation characteristics of light, a FRET quantification is also possible with only a single camera exposure.

CFP-YFP pairs

The most popular FRET pair for biological use is a cyan fluorescent protein (CFP) - yellow fluorescent protein (YFP) pair. Both are color variants of green fluorescent protein (GFP). While labeling with organic fluorescent dyes requires troublesome processes of purification, chemical modification, and intracellular injection of a host protein, GFP variants can be easily attached to a host protein by genetic engineering. By virtue of GFP variants, the use of FRET techniques for biological research is becoming more and more popular.



BRET

A limitation of FRET is the requirement for external illumination to initiate the fluorescence transfer, which can lead to background noise in the results from direct excitation of the acceptor or to photobleaching. To avoid this drawback, Bioluminescence Resonance Energy Transfer (or **BRET**) has been developed. This technique uses a bioluminescent luciferase (typically the luciferase from *Renilla reniformis*) rather than CFP to produce an initial photon emission compatible with YFP.

FRET and BRET are also the common tools in the study of biochemical reaction kinetics and molecular motors.

Photobleaching FRET

FRET efficiencies can also be inferred from the photobleaching rates of the donor in the presence and absence of an acceptor. This method can be performed on most fluorescence microscopes; one simply shines the excitation light (of a frequency that will excite the donor but not the acceptor significantly) on specimens with and without the acceptor fluorophore and monitors the donor fluorescence (typically separated from acceptor fluorescence using a bandpass filter) over time. The timescale is that of photobleaching, which is seconds to minutes, with fluorescence in each curve being given by

$$(\text{background}) + (\text{constant}) * e^{-(\text{time})/\tau_{\text{pb}}}$$

where τ_{pb} is the photobleaching decay time constant and depends on whether the acceptor is present or not. Since photobleaching consists in the permanent inactivation of excited fluorophores, resonance energy transfer from an excited donor to an acceptor fluorophore prevents the photobleaching of that donor fluorophore, and thus high FRET efficiency leads to a longer photobleaching decay time constant:

$$E = 1 - \tau_{\text{pb}}/\tau'_{\text{pb}}$$

where τ'_{pb} and τ_{pb} are the photobleaching decay time constants of the donor in the presence and in the absence of the acceptor, respectively. (Notice that the fraction is the reciprocal of that used for lifetime measurements). This technique was introduced by Jovin in 1989.^[7] Its use of an entire curve of points to extract the time constants can give it accuracy advantages over the other methods. Also, the fact that time measurements are over seconds rather than nanoseconds makes it easier than fluorescence lifetime measurements, and because photobleaching decay rates do not generally depend on donor concentration (unless acceptor saturation is an issue), the careful control of concentrations needed for intensity measurements is not needed. It is, however, important to keep the illumination the same for the with- and without-acceptor measurements, as photobleaching increases markedly with more intense incident light.

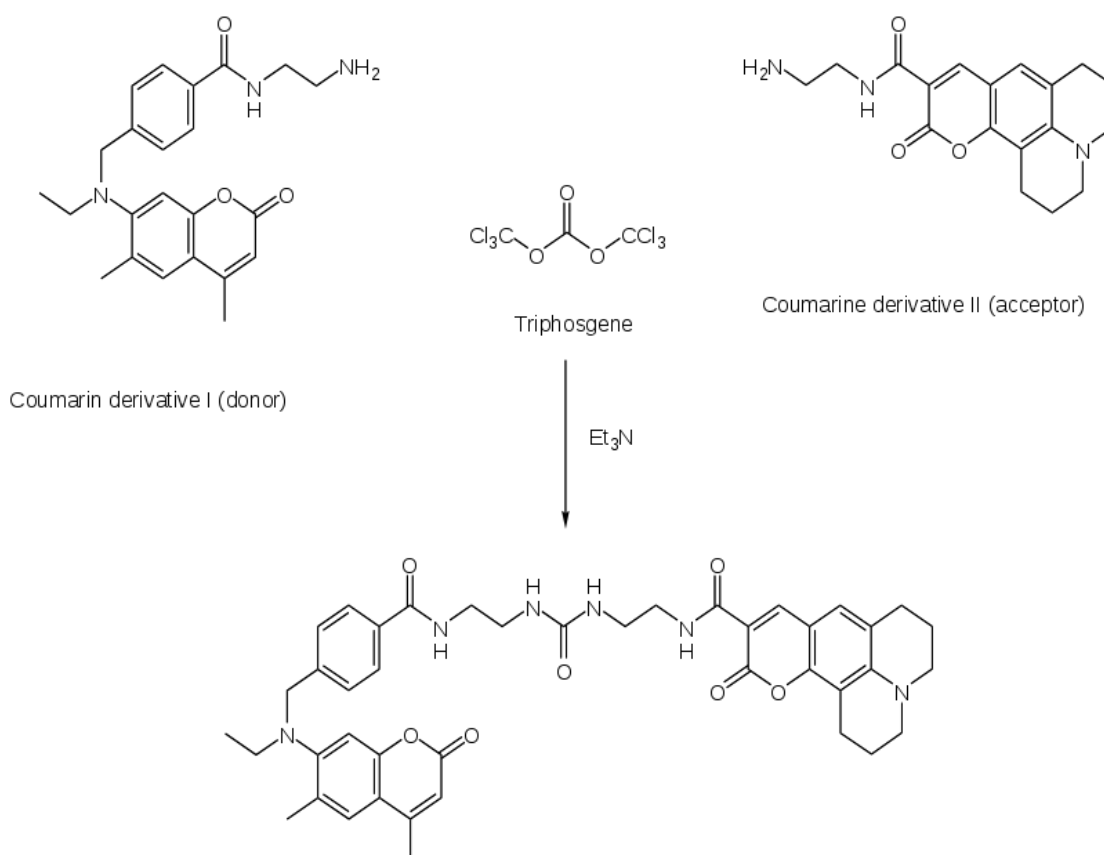
Other methods

A different, but related, mechanism is Dexter Electron Transfer.

An alternative method to detecting protein-protein proximity is the bimolecular fluorescence complementation (BiFC) where two halves of a YFP are fused to a protein. When these two halves meet they form a fluorophore after about 60 s - 1 hr.^[8]

Applications

FRET has been applied in an experimental method for the detection of phosgene. In it, phosgene or rather triphosgene as a safe substitute serves as a linker between an acceptor and a donor coumarine (forming urea groups).^[9] The presence of phosgene is detected at $5 \times 10^{-5} \text{ M}$ with a typical FRET emission at 464 nm.



FRET is also used to study lipid rafts in cell membranes.^[10]

See also

- Resonant energy transfer is used for remotely powering equipment such as smart cards
- Fluorescence principles / energy transfer (FRET): light emitted upon excitation by illumination at a shorter wavelength
- Bioluminescence principles / energy transfer (BRET): light emitted by a chemical enzymatic reaction (Luminol/Peroxidase, Luciferin/Luciferase, Coelenterazine/Aequorin)
- FCS

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Further reading

- doi:10.1016/S0959-440X(00)00190-1 Recent advances in FRET: distance determination in protein–DNA complexes. *Current Opinion in Structural Biology* **2001**, 11(2), 201-207

External links

- Browser-based calculator to find the critical distance and FRET efficiency with known spectral overlap (<http://www.calctool.org/CALC/chem/photochemistry/fret>)
- FRET description (<http://dwb.unl.edu/Teacher/NSF/C08/C08Links/pps99.cryst.bbk.ac.uk/projects/gmocz/fret.htm>)
- Fluorescence Resonance Energy Transfer (FRET) Microscopy (<http://www.olympusmicro.com/primer/techniques/fluorescence/fret/fretintro.html>)
- Lambert Instruments (<http://www.lambert-instruments.com/>)

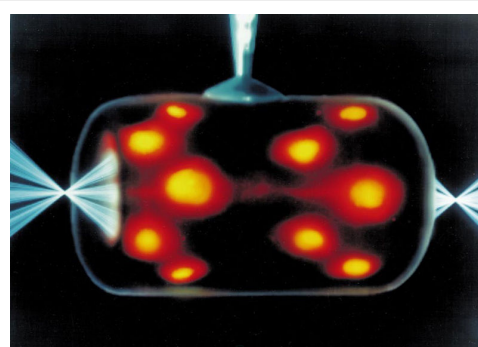
X-ray microscope

An **X-ray microscope** uses electromagnetic radiation in the soft X-ray band to produce images of very small objects. Unlike visible light, X-rays do not reflect or refract easily, and they are invisible to the human eye. Therefore the basic process of an X-ray microscope is to expose film or use a charge-coupled device (CCD) detector to detect X-rays that pass through the specimen. It is a contrast imaging technology using the difference in absorption of soft x-ray in the water window region (wavelength region: 2.3 - 4.4 nm, photon energy region: 0.28 - 0.53 keV) by the carbon atom (main element composing the living cell) and the oxygen atom (main element for water).

Early X-ray microscopes by Paul Kirkpatrick and Albert Baez used grazing-incidence reflective optics to focus the X-rays, which grazed X-rays off parabolic curved mirrors at a very high angle of incidence. An alternative method of focusing X-rays is to use a tiny fresnel zone plate of concentric gold or nickel rings on a silicon dioxide substrate. Sir Lawrence Bragg produced some of the first usable X-ray images with his apparatus in the late 1940's.

In the 1950's Newberry produced a shadow X-ray microscope which placed the specimen between the source and a target plate, this became the basis for the first commercial X-ray microscopes from the General Electric Company.

The Advanced Light Source (ALS)[1] in Berkeley CA is home to XM-1 (<http://www.cxro.lbl.gov/BL612/>), a full field soft X-ray microscope operated by the Center for X-ray Optics [2] and dedicated to various applications in modern nanoscience, such as nanomagnetic materials, environmental and materials sciences and biology. XM-1 uses an X-ray lens to focus X-rays on a CCD, in a manner similar to an optical microscope. XM-1 still holds the world record in spatial resolution with Fresnel zone plates down to 15nm and is able to combine high spatial resolution with a sub-100ps time resolution to study e.g. ultrafast spin dynamics.



Indirect drive laser inertial confinement fusion uses a "hohlraum" which is irradiated with laser beam cones from either side on its inner surface to bathe a fusion microcapsule inside with smooth high intensity X-rays.

The highest energy X-rays which penetrate the hohlraum can be visualized using an X-ray microscope such as here, where X-radiation is represented in orange/red.

The ALS is also home to the world's first soft x-ray microscope designed for biological and biomedical research. This new instrument, XM-2 was designed and built by scientists from the National Center for X-ray Tomography (<http://ncxt.lbl.gov>). XM-2 is capable of producing 3-Dimensional tomograms of cells.

Sources of soft X-rays suitable for microscopy, such as synchrotron radiation sources, have fairly low brightness of the required wavelengths, so an alternative method of image formation is scanning transmission soft X-ray microscopy. Here the X-rays are focused to a point and the sample is mechanically scanned through the produced focal spot. At each point the transmitted X-rays are recorded with a detector such as a proportional counter or an avalanche photodiode. This type of Scanning Transmission X-ray Microscope (STXM) was first developed by researchers at Stony Brook University and was employed at the National Synchrotron Light Source at Brookhaven National Laboratory.

The resolution of X-ray microscopy lies between that of the optical microscope and the electron microscope. It has an advantage over conventional electron microscopy in that it can view biological samples in their natural state. Electron microscopy is widely used to obtain images with nanometer level resolution but the relatively thick living cell cannot be observed as the sample has to be chemically fixed, dehydrated, embedded in resin, then sliced ultra thin. However, it should be mentioned that cryo-electron microscopy allows the observation of biological specimens in their hydrated natural state, albeit embedded in water ice. Until now, resolutions of 30 nanometer are possible using the Fresnel zone plate lens which forms the image using the soft x-rays emitted from a synchrotron. Recently, more researchers have begun to use the soft x-rays emitted from laser-produced plasma rather than synchrotron radiation.

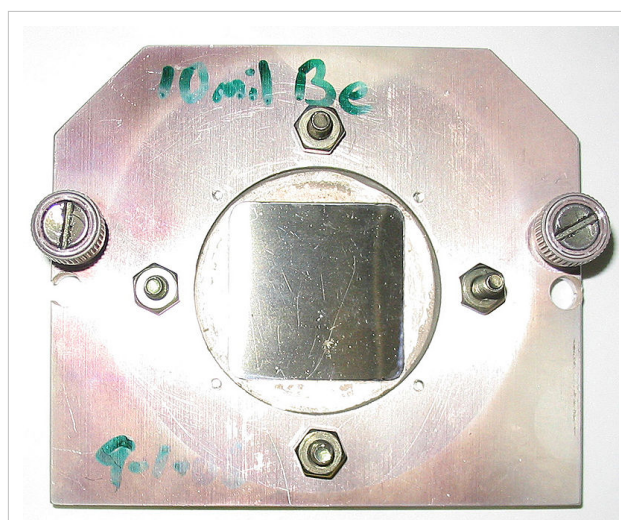
Additionally, X-rays cause fluorescence in most materials, and these emissions can be analyzed to determine the chemical elements of an imaged object. Another use is to generate diffraction patterns, a process used in X-ray crystallography. By analyzing the internal reflections of a diffraction pattern (usually with a computer program), the three-dimensional structure of a crystal can be determined down to the placement of individual atoms within its molecules. X-ray microscopes are sometimes used for these analyses because the samples are too small to be analyzed in any other way.

See also

- Synchrotron X-ray tomographic microscopy

External links

- Application of X-ray microscopy in analysis of living hydrated cells ^[3]
- Hard X-ray microbeam experiments with a sputtered-sliced Fresnel zone plate and its applications ^[4]
- Scientific applications of soft x-ray microscopy ^[5]



A square beryllium foil mounted in a steel case to be used as a window between a vacuum chamber and an X-ray microscope. Beryllium, due to its low Z number is highly transparent to X-rays.

References

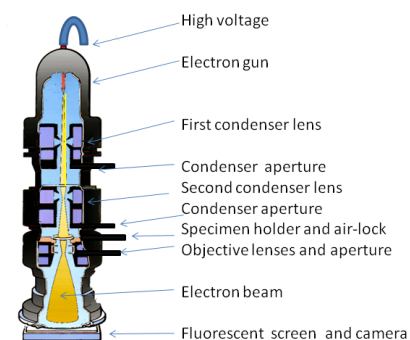
- [1] <http://www-als.lbl.gov>
- [2] <http://www.cxro.lbl.gov>
- [3] http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12379938
- [4] http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11972376
- [5] <http://www.cxro.lbl.gov/BL612/index.php?content=research.html>

Electron Microscope

An **electron microscope** is a type of microscope that produces an electronically-magnified image of a specimen for detailed observation. The electron microscope (EM) uses a particle beam of electrons to illuminate the specimen and create a magnified image of it. The microscope has a greater resolving power than a light-powered optical microscope, because it uses electrons that have wavelengths about 100,000 times shorter than visible light (photons), and can achieve magnifications of up to 2,000,000x, whereas light microscopes are limited to 2000x magnification.

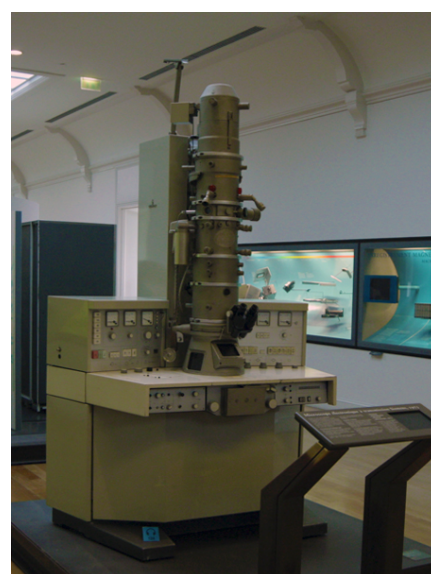
The electron microscope uses electrostatic and electromagnetic "lenses" to control the electron beam and focus it to form an image. These lenses are analogous to, but different from the glass lenses of an optical microscope that form a magnified image by focusing light on or through the specimen.

Electron microscopes are used to observe a wide range of biological and inorganic specimens including microorganisms, cells, large molecules, biopsy samples, metals, and crystals. Industrially, the electron microscope is primarily used for quality control and failure analysis in semiconductor device fabrication.



Transmission Electron Microscope

Diagram of a transmission electron microscope



A 1973 Siemens electron microscope, Musée des Arts et Métiers, Paris

History

In 1931, the German physicist Ernst Ruska and German electrical engineer Max Knoll constructed the prototype electron microscope, capable of four-hundred-power magnification; the apparatus was a practical application of the principles of electron microscopy.^[1] Two years later, in 1933, Ruska built an electron microscope that exceeded the resolution attainable with an optical (lens) microscope.^[1] Moreover, Reinhold Rudenberg, the scientific director of Siemens-Schuckertwerke, obtained the patent for the electron microscope in May 1931. Family illness compelled the electrical engineer to devise an electrostatic microscope, because he wanted to make visible the poliomyelitis virus.

In 1937, the Siemens company financed the development work of Ernst Ruska and Bodo von Borries, and employed Helmut Ruska (Ernst's brother) to develop applications for the microscope, especially with biologic specimens.^[1] ^[2] Also in 1937, Manfred von Ardenne pioneered the scanning electron microscope.^[3] The first *practical* electron microscope was constructed in 1938, at the University of Toronto, by Eli Franklin Burton and students Cecil Hall, James Hillier, and Albert Prebus; and Siemens produced the first *commercial* Transmission Electron Microscope (TEM) in 1939.^[4] Although contemporary electron microscopes are capable of two million-power magnification, as scientific instruments, they remain based upon Ruska's prototype.



Electron microscope constructed by Ernst Ruska in 1933

Types

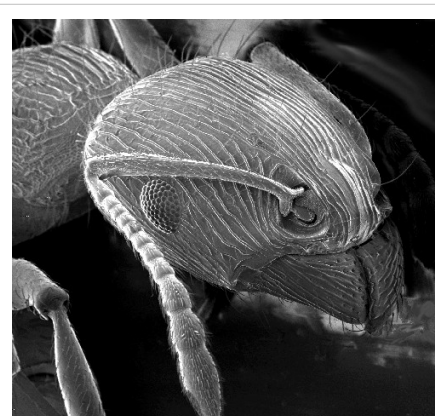
Transmission electron microscope (TEM)

The original form of electron microscope, the transmission electron microscope (TEM) uses a high voltage electron beam to create an image. The electrons are emitted by an electron gun, commonly fitted with a tungsten filament cathode as the electron source. The electron beam is accelerated by an anode typically at +100 keV (40 to 400 keV) with respect to the cathode, focused by electrostatic and electromagnetic lenses, and transmitted through the specimen that is in part transparent to electrons and in part scatters them out of the beam. When it emerges from the specimen, the electron beam carries information about the structure of the specimen that is magnified by the objective lens system of the microscope. The spatial variation in this information (the "image") is viewed by projecting the magnified electron image onto a fluorescent viewing screen coated with a phosphor or scintillator material such as zinc sulfide. The image can be photographically recorded by exposing a photographic film or plate directly to the electron beam, or a high-resolution phosphor may be coupled by means of a lens optical system or a fibre optic light-guide to the sensor of a CCD (charge-coupled device) camera. The image detected by the CCD may be displayed on a monitor or computer.

Resolution of the TEM is limited primarily by spherical aberration, but a new generation of aberration correctors have been able to partially overcome spherical aberration to increase resolution. Hardware correction of spherical aberration for the High Resolution TEM (HRTEM) has allowed the production of images with resolution below 0.5 Ångström (50 picometres)^[5] at magnifications above 50 million times.^[6] The ability to determine the positions of atoms within materials has made the HRTEM an important tool for nano-technologies research and development.^[7]

Scanning electron microscope (SEM)

Unlike the TEM, where electrons of the high voltage beam carry the image of the specimen, the electron beam of the Scanning Electron Microscope (SEM)^[8] does not at any time carry a complete image of the specimen. The SEM produces images by probing the specimen with a focused electron beam that is scanned across a rectangular area of the specimen (raster scanning). At each point on the specimen the incident electron beam loses some energy, and that lost energy is converted into other forms, such as heat, emission of low-energy secondary electrons, light emission (cathodoluminescence) or x-ray emission. The display of the SEM maps the varying intensity of any of these signals into the image in a position corresponding to the position of the beam on the specimen when the signal was generated. In the SEM image of an ant shown at right, the image was constructed from signals produced by a secondary electron detector, the normal or conventional imaging mode in most SEMs.



An image of an ant in a scanning electron microscope

Generally, the image resolution of an SEM is about an order of magnitude poorer than that of a TEM. However, because the SEM image relies on surface processes rather than transmission, it is able to image bulk samples up to many centimetres in size and (depending on instrument design and settings) has a great depth of field, and so can produce images that are good representations of the three-dimensional shape of the sample.

Reflection electron microscope (REM)

In the **Reflection Electron Microscope (REM)** as in the TEM, an electron beam is incident on a surface, but instead of using the transmission (TEM) or secondary electrons (SEM), the reflected beam of elastically scattered electrons is detected. This technique is typically coupled with Reflection High Energy Electron Diffraction (RHEED) and *Reflection high-energy loss spectrum (RHELS)*. Another variation is Spin-Polarized Low-Energy Electron Microscopy (SPLEEM), which is used for looking at the microstructure of magnetic domains.^[9]

Scanning transmission electron microscope (STEM)

The STEM rasters a focused incident probe across a specimen that (as with the TEM) has been thinned to facilitate detection of electrons scattered *through* the specimen. The high resolution of the TEM is thus possible in STEM. The focusing action (and aberrations) occur before the electrons hit the specimen in the STEM, but afterward in the TEM. The STEMs use of SEM-like beam rastering simplifies annular dark-field imaging, and other analytical techniques, but also means that image data is acquired in serial rather than in parallel fashion.

Low voltage electron microscope (LVEM)

The low voltage electron microscope (LVEM) is a combination of SEM, TEM and STEM in one instrument, which operates at relatively low electron accelerating voltage of 5 kV. Low voltage increases image contrast which is especially important for biological specimens. This increase in contrast significantly reduces, or even eliminates the need to stain. Sectioned samples generally need to be thinner than they would be for conventional TEM (20-65 nm). Resolutions of a few nm are possible in TEM, SEM and STEM modes.^{[10] [11]}

Sample preparation

Materials to be viewed under an electron microscope may require processing to produce a suitable sample. The technique required varies depending on the specimen and the analysis required:

- *Chemical fixation* for biological specimens aims to stabilize the specimen's mobile macromolecular structure by chemical crosslinking of proteins with aldehydes such as formaldehyde and glutaraldehyde, and lipids with osmium tetroxide.
- *Cryofixation* – freezing a specimen so rapidly, to liquid nitrogen or even liquid helium temperatures, that the water forms vitreous (non-crystalline) ice. This preserves the specimen in a snapshot of its solution state. An entire field called cryo-electron microscopy has branched from this technique. With the development of cryo-electron microscopy of vitreous sections (CEMOVIS), it is now possible to observe samples from virtually any biological specimen close to its native state.
- *Dehydration* – freeze drying, or replacement of water with organic solvents such as ethanol or acetone, followed by critical point drying or infiltration with embedding resins.
- *Embedding, biological specimens* – after dehydration, tissue for observation in the transmission electron microscope is embedded so it can be sectioned ready for viewing. To do this the tissue is passed through a 'transition solvent' such as epoxy propane and then infiltrated with a resin such as Araldite epoxy resin; tissues may also be embedded directly in water-miscible acrylic resin. After the resin has been polymerised (hardened) the sample is thin sectioned (ultrathin sections) and stained - it is then ready for viewing.
- *Embedding, materials* - after embedding in resin, the specimen is usually ground and polished to a mirror-like finish using ultra-fine abrasives. The polishing process must be performed carefully to minimize scratches and other polishing artifacts that reduce image quality.
- *Sectioning* – produces thin slices of specimen, semitransparent to electrons. These can be cut on an ultramicrotome with a diamond knife to produce ultrathin slices about 60-90 nm thick. Disposable glass knives are also used because they can be made in the lab and are much cheaper.
- *Staining* – uses heavy metals such as lead, uranium or tungsten to scatter imaging electrons and thus give contrast between different structures, since many (especially biological) materials are nearly "transparent" to electrons (weak phase objects). In biology, specimens are can be stained "en bloc" before embedding and also later after sectioning. Typically thin sections are stained for several minutes with an aqueous or alcoholic solution of uranyl acetate followed by aqueous lead citrate.
- *Freeze-fracture or freeze-etch* – a preparation method particularly useful for examining lipid membranes and their incorporated proteins in "face on" view. The fresh tissue or cell suspension is frozen rapidly (cryofixed), then fractured by simply breaking or by using a microtome while maintained at liquid nitrogen temperature. The cold fractured surface (sometimes "etched" by increasing the temperature to about -100°C for several minutes to let some ice sublime) is then shadowed with evaporated platinum or gold at an average angle of 45° in a high vacuum evaporator. A second coat of carbon, evaporated perpendicular to the average surface plane is often performed to improve stability of the replica coating. The specimen is returned to room temperature and pressure, then the extremely fragile "pre-shadowed" metal replica of the fracture surface is released from the underlying biological material by careful chemical digestion with acids, hypochlorite solution or SDS detergent. The still-floating replica is thoroughly washed from residual chemicals, carefully fished up on fine grids, dried then viewed in the TEM.



An insect coated in gold for viewing with a scanning electron microscope.

- *Ion Beam Milling* – thins samples until they are transparent to electrons by firing ions (typically argon) at the surface from an angle and sputtering material from the surface. A subclass of this is Focused ion beam milling, where gallium ions are used to produce an electron transparent membrane in a specific region of the sample, for example through a device within a microprocessor. Ion beam milling may also be used for cross-section polishing prior to SEM analysis of materials that are difficult to prepare using mechanical polishing.
- *Conductive Coating* – an ultrathin coating of electrically-conducting material, deposited either by high vacuum evaporation or by low vacuum sputter coating of the sample. This is done to prevent the accumulation of static electric fields at the specimen due to the electron irradiation required during imaging. Such coatings include gold, gold/palladium, platinum, tungsten, graphite etc. and are especially important for the study of specimens with the scanning electron microscope. Another reason for coating, even when there is more than enough conductivity, is to improve contrast, a situation more common with the operation of a FESEM (field emission SEM).

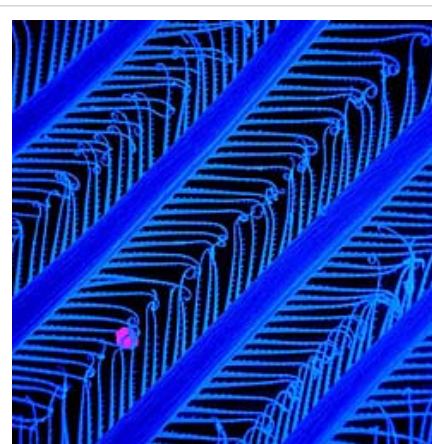
Disadvantages

Electron microscopes are expensive to build and maintain, but the capital and running costs of confocal light microscope systems now overlaps with those of basic electron microscopes. They are dynamic rather than static in their operation, requiring extremely stable high-voltage supplies, extremely stable currents to each electromagnetic coil/lens, continuously-pumped high- or ultra-high-vacuum systems, and a cooling water supply circulation through the lenses and pumps. As they are very sensitive to vibration and external magnetic fields, microscopes designed to achieve high resolutions must be housed in stable buildings (sometimes underground) with special services such as magnetic field cancelling systems. Some desktop low voltage electron microscopes have TEM capabilities at very low voltages (around 5 kV) without stringent voltage supply, lens coil current, cooling water or vibration isolation requirements and as such are much less expensive to buy and far easier to install and maintain, but do not have the same ultra-high (atomic scale) resolution capabilities as the larger instruments.

The samples largely have to be viewed in vacuum, as the molecules that make up air would scatter the electrons. One exception is the environmental scanning electron microscope, which allows hydrated samples to be viewed in a low-pressure (up to 20 Torr/2.7 kPa), wet environment.

Scanning electron microscopes usually image conductive or semi-conductive materials best. Non-conductive materials can be imaged by an environmental scanning electron microscope. A common preparation technique is to coat the sample with a several-nanometer layer of conductive material, such as gold, from a sputtering machine; however, this process has the potential to disturb delicate samples.

Small, stable specimens such as carbon nanotubes, diatom frustules and small mineral crystals (asbestos fibres, for example) require no special treatment before being examined in the electron microscope. Samples of hydrated materials, including almost all biological specimens have to be prepared in various ways to stabilize them, reduce their thickness (ultrathin sectioning) and increase their electron optical contrast (staining). These processes may result in *artifacts*, but these can usually be identified by comparing the results obtained by using radically different specimen preparation methods. It is generally believed by scientists working in the field that as results from various preparation techniques have been compared and that there is no reason that they should all produce similar artifacts, it is reasonable to believe that electron microscopy features correspond with those of living cells. In addition,



False-color SEM image of the filter setae of an Antarctic krill. (Raw electron microscope images carry no color information.)

Pictured: First degree filter setae with V-shaped second degree setae pointing towards the inside of the feeding basket. The purple ball is 1 μm in diameter.

higher-resolution work has been directly compared to results from X-ray crystallography, providing independent confirmation of the validity of this technique. Since the 1980s, analysis of cryofixed, vitrified specimens has also become increasingly used by scientists, further confirming the validity of this technique.^{[12] [13] [14]}

Applications

Semiconductor and data storage

- Circuit edit
- Defect analysis
- Failure analysis

Biology and life sciences

- Diagnostic electron microscopy
- Cryobiology
- Protein localization
- Electron tomography
- Cellular tomography
- Cryo-electron microscopy
- Toxicology
- Biological production and viral load monitoring
- Particle analysis
- Pharmaceutical QC
- Structural biology
- 3D tissue imaging
- Virology
- Vitrification

Research

- Electron beam-induced deposition
- Materials qualification
- Materials and sample preparation
- Nanoprototyping
- Nanometrology
- Device testing and characterization

Industry

- High-resolution imaging
- 2D & 3D micro-characterization
- Macro sample to nanometer metrology
- Particle detection and characterization
- Direct beam-writing fabrication
- Dynamic materials experiments
- Sample preparation
- Forensics
- Mining (mineral liberation analysis)
- Chemical/Petrochemical

See also

- Category:Electron microscope images
- Field emission microscope
- HiRISE
- Scanning tunneling microscope
- Transmission Electron Aberration-corrected Microscope
- *Ultramicroscopy* (journal)

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External links

- Science Aid: Electron Microscopy (<http://scienceaid.co.uk/biology/cell/analysingcells.html>) High School (GCSE, A Level) resource
- Cell Centered Database - Electron microscopy data (<http://ccdb.ucsd.edu/sand/main?typeid=4&event=showMPByType&start=1>)

General

- Nanohedron.com|Nano image gallery (<http://www.nanohedron.com/>) beautiful images generated with electron microscopes.
- electron microscopy (<http://www.microscopy.ethz.ch>) Website of the ETH Zurich: Very good graphics and images, which illustrate various procedures.
- Environmental Scanning Electron Microscope (ESEM) (<http://www.danilatos.com>)
- X-ray element analysis in electron microscope (http://www.microanalyst.net/index_e.phtml) – Information portal with X-ray microanalysis and EDX contents

History

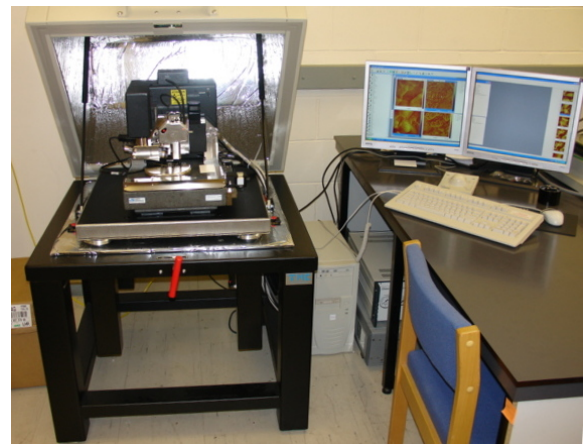
- John H.L. Watson: Very early Electron Microscopy in the Department of Physics, the University of Toronto – A personal recollection (<http://www.physics.utoronto.ca/overview/history/microsco>)
- Rubin Borasky Electron Microscopy Collection, 1930-1988 (<http://americanhistory.si.edu/archives/d8452.htm>) Archives Center, National Museum of American History, Smithsonian Institution.

Other

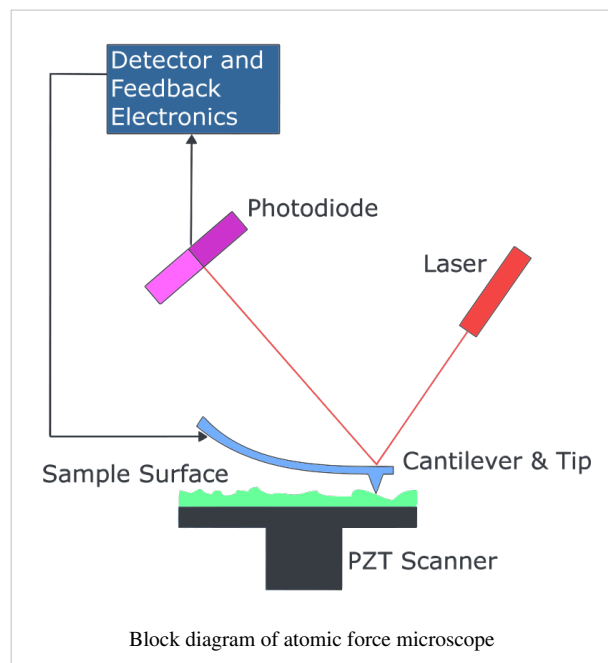
- The Royal Microscopical Society, Electron Microscopy Section (UK) (<http://www.rms.org.uk/em.shtml>)
- Albert Lleal micrograph. Scanning Electron Micrograph Coloured SEM (<http://www.albertlleal.com/microphotography.html>)

Atomic force microscope

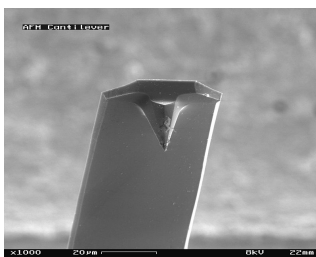
Atomic force microscopy (AFM) or scanning force microscopy (SFM) is a very high-resolution type of scanning probe microscopy, with demonstrated resolution on the order of fractions of a nanometer, more than 1000 times better than the optical diffraction limit. The precursor to the AFM, the scanning tunneling microscope, was developed by Gerd Binnig and Heinrich Rohrer in the early 1980s at IBM Research - Zurich, a development that earned them the Nobel Prize for Physics in 1986. Binnig, Quate and Gerber invented the first atomic force microscope (also abbreviated as AFM) in 1986. The first commercially available atomic force microscope was introduced in 1989. The AFM is one of the foremost tools for imaging, measuring, and manipulating matter at the nanoscale. The information is gathered by "feeling" the surface with a mechanical probe. Piezoelectric elements that facilitate tiny but accurate and precise movements on (electronic) command enable the very precise scanning. In some variations, electric potentials can also be scanned using conducting cantilevers. In newer more advanced versions, currents can even be passed through the tip to probe the electrical conductivity or transport of the underlying surface, but this is much more challenging with very few groups reporting reliable data.



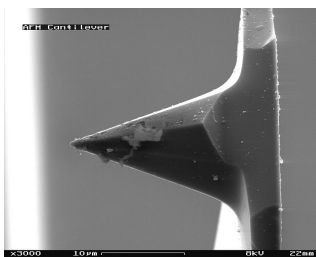
A commercial AFM setup



Basic principles



Electron micrograph of a used AFM cantilever image width ~100 micrometers...



and ~30 micrometers

The AFM consists of a cantilever with a sharp tip (probe) at its end that is used to scan the specimen surface. The cantilever is typically silicon or silicon nitride with a tip radius of curvature on the order of nanometers. When the tip is brought into proximity of a sample surface, forces between the tip and the sample lead to a deflection of the cantilever according to Hooke's law. Depending on the situation, forces that are measured in AFM include mechanical contact force, van der Waals forces, capillary forces, chemical bonding, electrostatic forces, magnetic forces (see magnetic force microscope, MFM), Casimir forces, solvation forces, etc. Along with force, additional quantities may simultaneously be measured through the use of specialized types of probe (see scanning thermal microscopy, photothermal microspectroscopy, etc.). Typically, the deflection is measured using a laser spot reflected from the top surface of the cantilever into an array of photodiodes. Other methods that are used include optical interferometry, capacitive sensing or piezoresistive AFM cantilevers. These cantilevers are fabricated with piezoresistive elements that act as a strain gauge. Using a Wheatstone bridge, strain in the AFM cantilever due to deflection can be measured, but this method is not as sensitive as laser deflection or interferometry.

If the tip was scanned at a constant height, a risk would exist that the tip collides with the surface, causing damage. Hence, in most cases a feedback mechanism is employed to adjust the tip-to-sample distance to maintain a constant force between the tip and the sample. Traditionally, the sample is mounted on a piezoelectric tube, that can move the sample in the z direction for maintaining a constant force, and the x and y directions for scanning the sample. Alternatively a 'tripod' configuration of three piezo crystals may be employed, with each responsible for scanning in the x , y and z directions. This eliminates some of the distortion effects seen with a tube scanner. In newer designs, the tip is mounted on a vertical piezo scanner while the sample is being scanned in X and Y using another piezo block. The resulting map of the area $s = f(x,y)$ represents the topography of the sample.

The AFM can be operated in a number of modes, depending on the application. In general, possible imaging modes are divided into static (also called *contact*) modes and a variety of dynamic (or non-contact) modes where the cantilever is vibrated.

Imaging modes

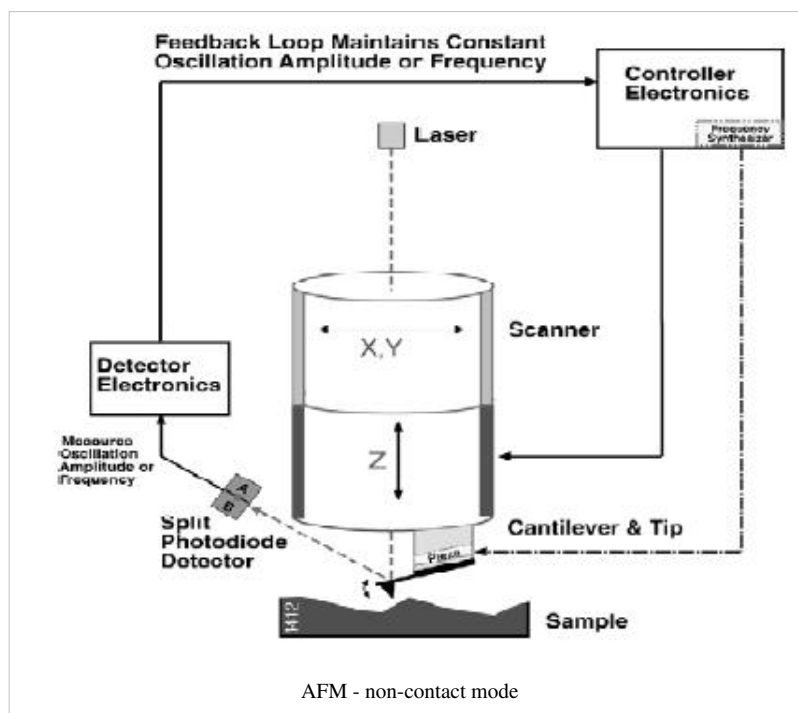
The primary modes of operation for an AFM are static mode and dynamic mode. In static mode, the cantilever is "dragged" across the surface of the sample and the contours of the surface are measured directly using the deflection of the cantilever. In the dynamic mode, the cantilever is externally oscillated at or close to its fundamental resonance frequency or a harmonic. The oscillation amplitude, phase and resonance frequency are modified by tip-sample interaction forces. These changes in oscillation with respect to the external reference oscillation provide information about the sample's characteristics.

Contact mode

In the static mode operation, the static tip deflection is used as a feedback signal. Because the measurement of a static signal is prone to noise and drift, low stiffness cantilevers are used to boost the deflection signal. However, close to the surface of the sample, attractive forces can be quite strong, causing the tip to "snap-in" to the surface. Thus static mode AFM is almost always done in contact where the overall force is repulsive. Consequently, this technique is typically called "contact mode". In contact mode, the force between the tip and the surface is kept constant during scanning by maintaining a constant deflection.

Non-contact mode

In this mode, the tip of the cantilever does not contact the sample surface. The cantilever is instead oscillated at a frequency slightly above its resonance frequency where the amplitude of oscillation is typically a few nanometers (<10 nm). The van der Waals forces, which are strongest from 1 nm to 10 nm above the surface, or any other long range force which extends above the surface acts to decrease the resonance frequency of the cantilever. This decrease in resonance frequency combined with the feedback loop system maintains a constant oscillation amplitude or frequency by adjusting the average tip-to-sample distance. Measuring the tip-to-sample distance at each (x,y) data point allows the scanning software to construct a topographic image of the sample surface.



Non-contact mode AFM does not suffer from tip or sample degradation effects that are sometimes observed after taking numerous scans with contact AFM. This makes non-contact AFM preferable to contact AFM for measuring soft samples. In the case of rigid samples, contact and non-contact images may look the same. However, if a few monolayers of adsorbed fluid are lying on the surface of a rigid sample, the images may look quite different. An AFM operating in contact mode will penetrate the liquid layer to image the underlying surface, whereas in non-contact mode an AFM will oscillate above the adsorbed fluid layer to image both the liquid and surface.

Schemes for dynamic mode operation include frequency modulation and the more common amplitude modulation. In frequency modulation, changes in the oscillation frequency provide information about tip-sample interactions. Frequency can be measured with very high sensitivity and thus the frequency modulation mode allows for the use of very stiff cantilevers. Stiff cantilevers provide stability very close to the surface and, as a result, this technique was the first AFM technique to provide true atomic resolution in ultra-high vacuum conditions.^[1]

In amplitude modulation, changes in the oscillation amplitude or phase provide the feedback signal for imaging. In amplitude modulation, changes in the phase of oscillation can be used to discriminate between different types of materials on the surface. Amplitude modulation can be operated either in the non-contact or in the intermittent contact regime. In dynamic contact mode, the cantilever is oscillated such that the separation distance between the cantilever tip and the sample surface is modulated.

Amplitude modulation has also been used in the non-contact regime to image with atomic resolution by using very stiff cantilevers and small amplitudes in an ultra-high vacuum environment.

Tapping mode

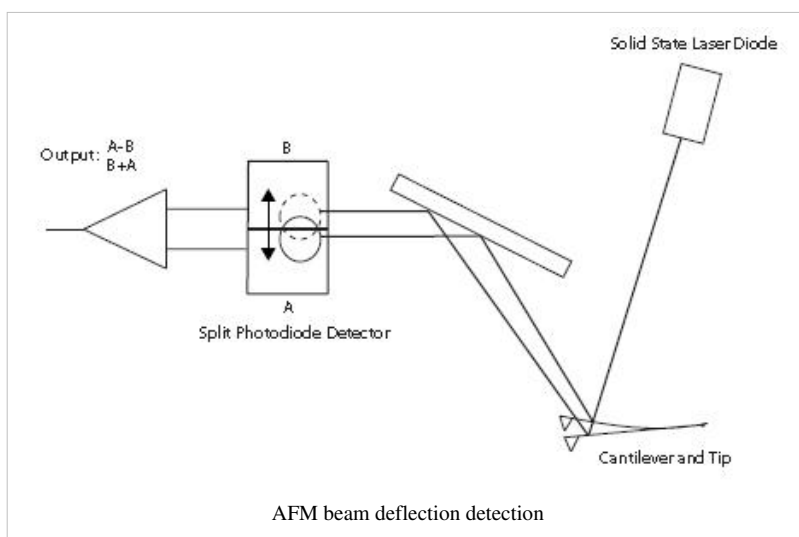
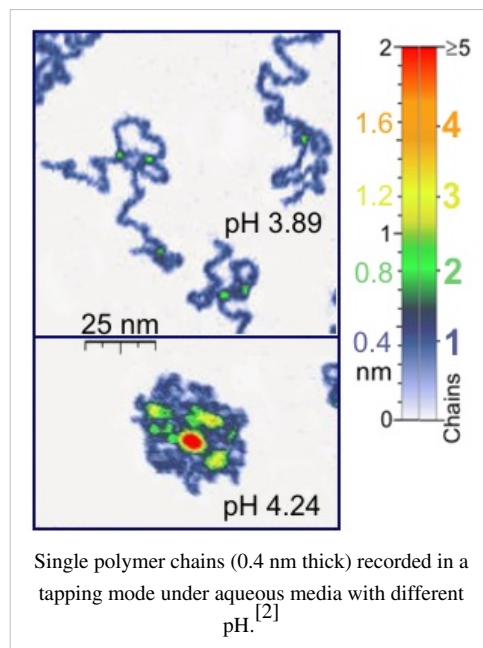
In ambient conditions, most samples develop a liquid meniscus layer. Because of this, keeping the probe tip close enough to the sample for short-range forces to become detectable while preventing the tip from sticking to the surface presents a major problem for non-contact dynamic mode in ambient conditions. Dynamic contact mode (also called intermittent contact or tapping mode) was developed to bypass this problem.^[3]

In *tapping mode*, the cantilever is driven to oscillate up and down at near its resonance frequency by a small piezoelectric element mounted in the AFM tip holder similar to non-contact mode. However, the amplitude of this oscillation is greater than 10 nm, typically 100 to 200 nm. Due to the interaction of forces acting on the cantilever when the tip comes close to the surface, Van der Waals force, dipole-dipole interaction, electrostatic forces, etc cause the amplitude of this oscillation to decrease as the tip gets closer to the sample. An electronic servo uses the piezoelectric actuator to control the height of the cantilever above the sample. The servo adjusts the height to maintain a set cantilever oscillation amplitude as the cantilever is scanned over the sample. A *tapping AFM* image is therefore produced by imaging the force of the intermittent contacts of the tip with the sample surface.

This method of "tapping" lessens the damage done to the surface and the tip compared to the amount done in contact mode. Tapping mode is gentle enough even for the visualization of supported lipid bilayers or adsorbed single polymer molecules (for instance, 0.4 nm thick chains of synthetic polyelectrolytes) under liquid medium. With proper scanning parameters, the conformation of single molecules can remain unchanged for hours.^[2]

AFM cantilever deflection measurement

Laser light from a solid state diode is reflected off the back of the cantilever and collected by a position sensitive detector (PSD) consisting of two closely spaced photodiodes whose output signal is collected by a differential amplifier. Angular displacement of cantilever results in one photodiode collecting more light than the other photodiode, producing an output signal (the difference between the photodiode signals normalized by their sum) which is proportional to the deflection of the cantilever. It detects cantilever deflections <10 nm (thermal noise limited). A long beam path (several centimeters) amplifies changes in beam angle.



Force spectroscopy

Another major application of AFM (besides imaging) is force spectroscopy, the direct measurement of tip-sample interaction forces as a function of the gap between the tip and sample (the result of this measurement is called a force-distance curve). For this method, the AFM tip is extended towards and retracted from the surface as the deflection of the cantilever is monitored as a function of piezoelectric displacement. These measurements have been used to measure nanoscale contacts, atomic bonding, Van der Waals forces, and Casimir forces, dissolution forces in liquids and single molecule stretching and rupture forces.^[4] Furthermore, AFM was used to measure in aqueous environment dispersion force due to polymer adsorbed on the substrate.^[5] Forces of the order of a few piconewtons can now be routinely measured with a vertical distance resolution of better than 0.1 nanometer. Force spectroscopy can be performed with either static or dynamic modes. In dynamic modes, information about the cantilever vibration is monitored in addition to the static deflection.^[6]

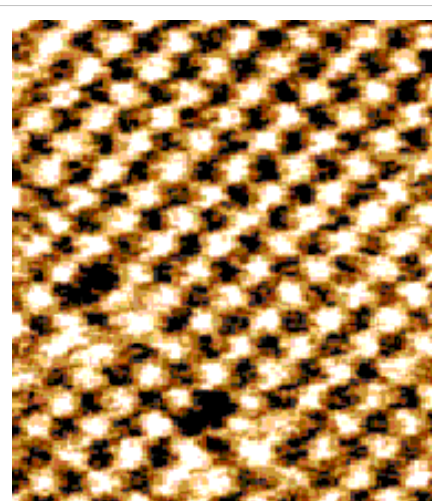
Problems with the technique include no direct measurement of the tip-sample separation and the common need for low stiffness cantilevers which tend to 'snap' to the surface. The snap-in can be reduced by measuring in liquids or by using stiffer cantilevers, but in the latter case a more sensitive deflection sensor is needed. By applying a small dither to the tip, the stiffness (force gradient) of the bond can be measured as well.^[7]

Identification of individual surface atoms

The AFM can be used to image and manipulate atoms and structures on a variety of surfaces. The atom at the apex of the tip "senses" individual atoms on the underlying surface when it forms incipient chemical bonds with each atom. Because these chemical interactions subtly alter the tip's vibration frequency, they can be detected and mapped. This principle was used to distinguish between atoms of silicon, tin and lead on an alloy surface, by comparing these 'atomic fingerprints' to values obtained from large-scale density functional theory (DFT) simulations.^[8]

The trick is to first measure these forces precisely for each type of atom expected in the sample, and then to compare with forces given by DFT simulations. The team found that the tip interacted most strongly with silicon atoms, and interacted 23% and 41% less strongly with tin and lead atoms, respectively. Thus, each different type of atom can be identified in the matrix as the tip is moved across the surface.

Such a technique has been used now in biology and extended recently to cell biology. Forces corresponding to (i) the unbinding of receptor ligand couples (ii) unfolding of proteins (iii) cell adhesion at single cell scale have been gathered.



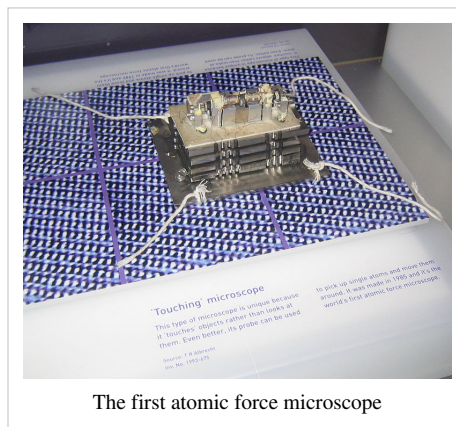
The atoms of a sodium chloride crystal viewed with an atomic force microscope

Advantages and disadvantages

Just like any other tool, an AFM's usefulness has limitations. When determining whether or not analyzing a sample with an AFM is appropriate, there are various advantages and disadvantages that must be considered.

Advantages

AFM has several advantages over the scanning electron microscope (SEM). Unlike the electron microscope which provides a two-dimensional projection or a two-dimensional image of a sample, the AFM provides a three-dimensional surface profile. Additionally, samples viewed by AFM do not require any special treatments (such as metal/carbon coatings) that would irreversibly change or damage the sample. While an electron microscope needs an expensive vacuum environment for proper operation, most AFM modes can work perfectly well in ambient air or even a liquid environment. This makes it possible to study biological macromolecules and even living organisms. In principle, AFM can provide higher resolution than SEM. It has been shown to give true atomic resolution in ultra-high vacuum (UHV) and, more recently, in liquid environments. High resolution AFM is comparable in resolution to scanning tunneling microscopy and transmission electron microscopy.



The first atomic force microscope

Disadvantages

A disadvantage of AFM compared with the scanning electron microscope (SEM) is the single scan image size. In one pass, the SEM can image an area on the order of square millimeters with a depth of field on the order of millimeters. Whereas the AFM can only image a maximum height on the order of 10-20 micrometers and a maximum scanning area of about 150×150 micrometers. One method of improving the scanned area size for AFM is by using parallel probes in a fashion similar to that of millipede data storage.

The scanning speed of an AFM is also a limitation. Traditionally, an AFM cannot scan images as fast as a SEM, requiring several minutes for a typical scan, while a SEM is capable of scanning at near real-time, although at relatively low quality. The relatively slow rate of scanning during AFM imaging often leads to thermal drift in the image^{[9] [10]} making the AFM microscope less suited for measuring accurate distances between topographical features on the image. However, several fast-acting designs^{[11] [12]} were suggested to increase microscope scanning productivity including what is being termed videoAFM (reasonable quality images are being obtained with videoAFM at video rate: faster than the average SEM). To eliminate image distortions induced by thermal drift, several methods have been introduced.^{[9] [10]}

AFM images can also be affected by hysteresis of the piezoelectric material^[13] and cross-talk between the x , y , z axes that may require software enhancement and filtering. Such filtering could "flatten" out real topographical features. However, newer AFMs utilize closed-loop scanners which practically eliminate these problems. Some AFMs also use separated orthogonal scanners (as opposed to a single tube) which also serve to eliminate part of the cross-talk problems.

As with any other imaging technique, there is the possibility of image artifacts, which could be induced by an unsuitable tip, a poor operating environment, or even by the sample itself. These image artifacts are unavoidable however, their occurrence and effect on results can be reduced through various methods.

Due to the nature of AFM probes, they cannot normally measure steep walls or overhangs. Specially made cantilevers and AFMs can be used to modulate the probe sideways as well as up and down (as with dynamic contact and non-contact modes) to measure sidewalls, at the cost of more expensive cantilevers, lower lateral resolution and additional artifacts.

Piezoelectric scanners

AFM scanners are made from piezoelectric material, which expands and contracts proportionally to an applied voltage. Whether they elongate or contract depends upon the polarity of the voltage applied. The scanner is constructed by combining independently operated piezo electrodes for X, Y, and Z into a single tube, forming a scanner which can manipulate samples and probes with extreme precision in 3 dimensions.

Scanners are characterized by their sensitivity which is the ratio of piezo movement to piezo voltage, i.e., by how much the piezo material extends or contracts per applied volt. Because of differences in material or size, the sensitivity varies from scanner to scanner. Sensitivity varies non-linearly with respect to scan size. Piezo scanners exhibit more sensitivity at the end than at the beginning of a scan. This causes the forward and reverse scans to behave differently and display hysteresis^[13] between the two scan directions. This can be corrected by applying a non-linear voltage to the piezo electrodes to cause linear scanner movement and calibrating the scanner accordingly.^[13]

The sensitivity of piezoelectric materials decreases exponentially with time. This causes most of the change in sensitivity to occur in the initial stages of the scanner's life. Piezoelectric scanners are run for approximately 48 hours before they are shipped from the factory so that they are past the point where they may have large changes in sensitivity. As the scanner ages, the sensitivity will change less with time and the scanner would seldom require recalibration.^[14]

See also

- Frictional force mapping
- Scanning tunneling microscope
- Scanning probe microscopy
- Scanning voltage microscopy
- Surface force apparatus

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External links

- ME 597/PHYS 570: Fundamentals of Atomic Force Microscopy (<http://nanohub.org/resources/7320>)
- DoITPoMS Teaching and Learning Package - Atomic Force Microscopy (<http://www.doitpoms.ac.uk/tlplib/afm/index.php>)

Further reading

- SPM - Scanning Probe Microscopy Website (<http://www.mobot.org/jwcross/spm/>)
- Atomic Force Microscopy resource library (<http://www.afmuniversity.org>)
- R. W. Carpick and M. Salmeron, Scratching the surface: Fundamental investigations of tribology with atomic force microscopy (<http://dx.doi.org/10.1021/cr960068q>), *Chemical Reviews*, vol. 97, iss. 4, pp. 1163–1194 (2007).

Neutron scattering

Neutron scattering encompasses all scientific techniques whereby the deflection of neutron radiation is used as a scientific probe. Neutrons readily interact with atomic nuclei and magnetic fields from unpaired electrons, making a useful probe of both structure and magnetic order. Neutron Scattering falls into two basic categories - elastic and inelastic. Elastic scattering is when a neutron interacts with a nucleus or electronic magnetic field but does not leave it in an excited state, meaning the emitted neutron has the same energy as the injected neutron. Scattering processes that involve an energetic excitation or relaxation by the neutron are inelastic: the injected neutron's energy is used or increased to create an excitation or by absorbing the excess energy from a relaxation, and consequently the emitted neutron's energy is reduced or increased respectively.

For several good reasons, moderated neutrons provide an ideal tool for the study of almost all forms of condensed matter. Firstly, they are readily produced at a nuclear research reactor or a spallation source. Normally in such processes neutrons are however produced with much higher energies than are needed. Therefore moderators are generally used which slow the neutrons down and therefore produce wavelengths that are comparable to the atomic spacing in solids and liquids, and kinetic energies that are comparable to those of dynamic processes in materials. Moderators can be made from aluminium and filled with liquid hydrogen (for very long wavelength neutrons) or liquid methane (for shorter wavelength neutrons). Fluxes of $10^7/\text{s}$ - $10^8/\text{s}$ are not atypical in most neutron sources from any given moderator.

The neutrons cause pronounced interference and energy transfer effects in scattering experiments. Unlike an x-ray photon with a similar wavelength, which interacts with the electron cloud surrounding the nucleus, neutrons interact with the nucleus itself. Because the neutron is an electrically neutral particle, it is deeply penetrating, and is therefore more able to probe the bulk material. Consequently, it enables the use of a wide range of sample environments that

are difficult to use with synchrotron x-ray sources. It also has the advantage that the cross sections for interaction do not increase with atomic number as they do with radiation from a synchrotron x-ray source. Thus neutrons can be used to analyse materials with low atomic numbers like proteins and surfactants. This can be done at synchrotron sources but very high intensities are needed which may cause the structures to change. Moreover, the nucleus provides a very short range, isotropic potential varying randomly from isotope to isotope, making it possible to tune the nuclear scattering contrast to suit the experiment:

The neutron has an additional advantage over the x-ray photon in the study of condensed matter. It readily interacts with internal magnetic fields in the sample. In fact, the strength of the magnetic scattering signal is often very similar to that of the nuclear scattering signal in many materials, which allows the simultaneous exploration of both nuclear and magnetic structure. Because the neutron scattering amplitude can be measured in absolute units, both the structural and magnetic properties as measured by neutrons can be compared quantitatively with the results of other characterisation techniques.

See also

- Neutron diffraction
 - Small angle neutron scattering
 - Neutron Reflectometry
- Inelastic neutron scattering
 - neutron triple-axis spectrometry
 - neutron time-of-flight scattering
 - neutron backscattering
 - neutron spin echo
 - neutron resonance spin echo
- Neutron scattering facilities

Applications

Neutron scattering has been used to study various vibration modes,^[1] including low-frequency collective motion in proteins and DNA,^{[2] [3] [4] [5] [6]} as reviewed by Dr. P. Martel in 1992.^[1]

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External links

- Neutron Scattering - A primer (<http://knocknick.files.wordpress.com/2008/04/neutrons-a-primer-by-rogen-pynn.pdf>) (LANL-hosted black and white version (<http://library.lanl.gov/cgi-bin/getfile?00326651.pdf>)) - An introductory article written by Roger Pynn (Los Alamos National Laboratory)
- Podcast Interview with two ILL scientists about neutron science/scattering at the ILL (<http://omegataupodcast.net/2010/03/28-neutron-science-at-the-ill/>)

ISIS neutron source

ISIS is a pulsed neutron and muon source. It is situated at the Rutherford Appleton Laboratory on the Harwell Science and Innovation Campus in Oxfordshire, United Kingdom and is part of the Science and Technology Facilities Council . It uses the techniques muon spectroscopy and neutron scattering to probe the structure and dynamics of condensed matter on a microscopic scale ranging from the subatomic to the macromolecular.

Hundreds of experiments are performed annually at ISIS by visiting researchers from around the world, in diverse science areas including physics, chemistry, materials engineering, earth sciences, biology and archaeology.

Neutrons and muons

Neutrons are uncharged constituents of atoms and penetrate materials well, deflecting only from the nuclei of atoms. The statistical accumulation of deflected neutrons at different positions beyond the

sample can be used to find the structure of a material, and the loss or gain of energy by neutrons can reveal the dynamic behaviour of parts of a sample, for example diffusive processes in solids. At ISIS the neutrons are created by accelerating 'bunches' of protons in a synchrotron, then colliding these with a heavy tantalum metal target, under a constant cooling load to dissipate the heat from the 160 kW proton beam. The impacts cause neutrons to spall off the tantalum atoms, and the neutrons are channelled through guides, or beamlines, to about 20 instruments, individually optimised for the study of different types of matter. The target station and most of the instruments are set in a large hall. Neutrons are a dangerous form of radiation, so the target and beamlines are heavily shielded with concrete.

ISIS produces muons by colliding a fraction of the proton beam with a graphite target, producing pions which decay rapidly into muons, delivered in a spin-polarised beam to sample stations.



ISIS experimental hall for Target Station 1

Science at ISIS

ISIS is administered and operated by the Science and Technology Facilities Council (previously CCLRC). Experimental time is open to academic users from funding countries and is applied for through a twice-yearly 'call for proposals'. Research allocation, or 'beam-time', is allotted to applicants via a peer-review process. Users and their parent institutions do not pay for

the running costs of the facility, which are as much as £11,000 per instrument per day. Their transport and living costs are also refunded whilst carrying out the experiment. Most users stay in Ridgeway House, a hotel near the site, or at Cosener's House, an STFC-run conference centre in Abingdon. Over 600 experiments by 1600 users are completed every year.

A large number of support staff operate the facility, aid users, and carry out research, the control room is staffed 24 hours a day, every day of the year. Instrument scientists oversee the running of each instrument and liaise with users, and other divisions provide sample environment, data analysis and computing expertise, maintain the accelerator, and run education programmes.

Among the important and pioneering work carried out was the discovery of the structure of high-temperature superconductors and the solid phase of buckminsterfullerene.

Construction for a second target station started in 2003, and the first neutrons were delivered to the target on December 14, 2007^[1]. It will use low-energy neutrons to study soft condensed matter, biological systems, advanced composites and nanomaterials. To supply the extra protons for this, the accelerator is being upgraded.

History and background of ISIS

The source was approved in 1977 for the RAL site on the Harwell campus and recycled components from earlier UK science programmes including the accelerator hall which had previously been occupied by the Nimrod accelerator. The first beam was produced in 1984, and the facility was formally opened by the then Prime Minister Margaret Thatcher in October 1985.^[2]

The name ISIS is not an acronym: it refers to the Ancient Egyptian goddess and the local name for the River Thames. The name was selected for the official opening of the facility in 1985, prior to this it was known as the SNS, or Spallation Neutron Source. The name was considered appropriate as Isis was a goddess who could restore life to the dead, and ISIS made use of equipment previously constructed for the Nimrod and Nina accelerators^[3].



Another view of the ISIS experimental hall for Target Station 1

External links

- ISIS facility ^[4]
- ISIS Second Target Station ^[5]
- The Science and Technology Facilities Council ^[6]

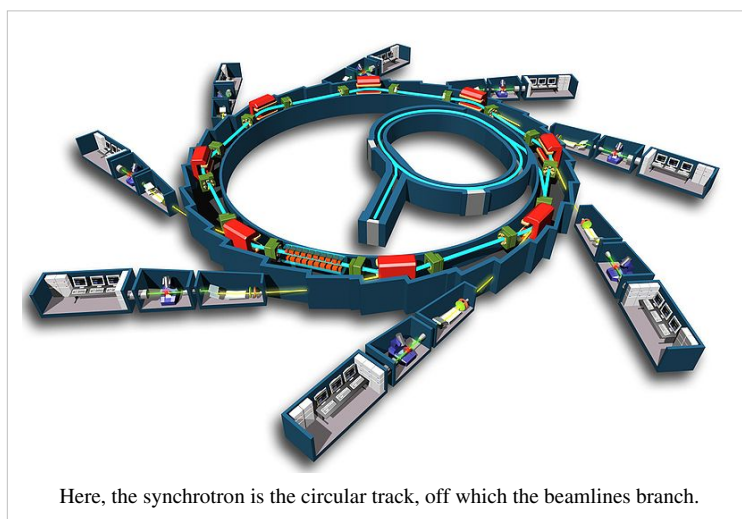
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- [5] <http://www.isis.stfc.ac.uk/about-isis/target-station-2/>
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Geographical coordinates: 51°34'18"N 1°19'12"W

Synchrotron

A **synchrotron** is a particular type of cyclic particle accelerator in which the magnetic field (to turn the particles so they circulate) and the electric field (to accelerate the particles) are carefully synchronised with the travelling particle beam. The proton synchrotron was originally conceived by Sir Marcus Oliphant^[1]. The honour of being the first to publish the idea went to Vladimir Veksler, and the first electron synchrotron was constructed by Edwin McMillan.



Characteristics

While a cyclotron uses a constant magnetic field and a constant-frequency applied electric field (one of these is varied in the synchrocyclotron), both of these fields are varied in the synchrotron. By increasing these parameters appropriately as the particles gain energy, their path can be held constant as they are accelerated. This allows the vacuum chamber for the particles to be a large thin torus. In reality it is easier to use some straight sections between the bending magnets and some bent sections within the magnets giving the torus the shape of a round-cornered polygon. A path of large effective radius may thus be constructed using simple straight and curved pipe segments, unlike the disc-shaped chamber of the cyclotron type devices. The shape also allows and requires the use of multiple magnets to bend the particle beams. Straight sections are required at spacings around a ring for both radiofrequency cavities, and in third generation setups space is allowed for insertion of energy extraction devices such as wigglers and undulators.

The maximum energy that a cyclic accelerator can impart is typically limited by the strength of the magnetic field(s) and the minimum radius (maximum curvature) of the particle path.

In a cyclotron the maximum radius is quite limited as the particles start at the center and spiral outward, thus the entire path must be a self-supporting disc-shaped evacuated chamber. Since the radius is limited, the power of the machine becomes limited by the strength of the magnetic field. In the case of an ordinary electromagnet the field strength is limited by the saturation of the core (when all

magnetic domains are aligned the field may not be further increased to any practical extent). The arrangement of the single pair of magnets the full width of the device also limits the economic size of the device.



The interior of the Australian Synchrotron facility. Dominating the image is the storage ring, showing the optical diagnostic beamline at front right. In the middle of the storage ring is the booster synchrotron and linac

Synchrotrons overcome these limitations, using a narrow beam pipe which can be surrounded by much smaller and more tightly focusing magnets. The ability of this device to accelerate particles is limited by the fact that the particles must be charged to be accelerated at all, but charged particles under acceleration emit photons (light), thereby losing energy. The limiting beam energy is reached when the energy lost to the lateral acceleration required to maintain the beam path in a circle equals the energy added each cycle. More powerful accelerators are built by using large radius paths and by using more numerous and more powerful microwave cavities to accelerate the particle beam between corners. Lighter particles (such as electrons) lose a larger fraction of their energy when turning. Practically speaking, the energy of electron/positron accelerators is limited by this radiation loss, while it does not play a significant role in the dynamics of proton or ion accelerators. The energy of those is limited strictly by the strength of magnets and by the cost.

Design and operation

Particles are injected into the main ring at substantial energies by either a linear accelerator or by an intermediate synchrotron which is in turn fed by a linear accelerator. The "linac" is in turn fed by particles accelerated to intermediate energy by a simple high voltage power supply, typically a Cockcroft-Walton generator.

Starting from an appropriate initial value determined by the injection velocity the magnetic field is then increased. The particles pass through an electrostatic accelerator driven by a high alternating voltage. At particle speeds not close to the speed of light the frequency of the accelerating voltage can be made roughly proportional to the current in the bending magnets. A finer control of the frequency is performed by a servo loop which responds to the detection of the passing of the traveling group of particles. At particle speeds approaching light speed the frequency becomes more nearly constant, while the current in the bending magnets continues to increase. The maximum energy that can be applied to the particles (for a given ring size and magnet count) is determined by the saturation of the cores of the bending magnets (the point at which increasing current does not produce additional magnetic field). One way to obtain additional power is to make the torus larger and add additional bending magnets. This allows the amount of particle redirection at saturation to be less and so the particles can be more energetic. Another means of obtaining higher power is to use superconducting magnets, these not being limited by core saturation.

Large synchrotrons

One of the early large synchrotrons, now retired, is the Bevatron, constructed in 1950 at the Lawrence Berkeley Laboratory. The name of this proton accelerator comes from its power, in the range of 6.3 GeV (then called BeV for billion electron volts; the name predates the adoption of the SI prefix giga-). A number of heavy elements, unseen in the natural world, were first created with this machine. This site is also the location of one of the first large bubble chambers used to examine the results of the atomic collisions produced here.



Modern industrial-scale synchrotrons can be very large (here, Soleil near Paris)

Another early large synchrotron is the Cosmotron built at Brookhaven National Laboratory which reached 3.3 GeV in 1953.^[2]

Until August 2008, the highest energy synchrotron in the world was the Tevatron, at the Fermi National Accelerator Laboratory, in the United States. It accelerates protons and antiprotons to slightly less than 1 TeV of kinetic energy and collides them together. The Large Hadron Collider (LHC), which has been built at the European Laboratory for High Energy Physics (CERN), has roughly seven times this energy (so proton-proton collisions occur at roughly 14 TeV). It is housed in the 27 km tunnel which formerly housed the Large Electron Positron (LEP) collider, so it will maintain the claim as the largest scientific device ever built. The LHC will also accelerate heavy ions (such as lead) up to an energy of 1.15 PeV.

The largest device of this type seriously proposed was the Superconducting Super Collider (SSC), which was to be built in the United States. This design, like others, used superconducting magnets which allow more intense magnetic fields to be created without the limitations of core saturation. While construction was begun, the project was cancelled in 1994, citing excessive budget overruns — this was due to naïve cost estimation and economic management issues rather than any basic engineering flaws. It can also be argued that the end of the Cold War resulted in a change of scientific funding priorities that contributed to its ultimate cancellation. While there is still potential for yet more powerful proton and heavy particle cyclic accelerators, it appears that the next step up in electron beam energy must avoid losses due to synchrotron radiation. This will require a return to the linear accelerator, but with devices significantly longer than those currently in use. There is at present a major effort to design and build the International Linear Collider (ILC), which will consist of two opposing linear accelerators, one for electrons and one for positrons. These will collide at a total center of mass energy of 0.5 TeV.

However, synchrotron radiation also has a wide range of applications (see synchrotron light) and many 2nd and 3rd generation synchrotrons have been built especially to harness it. The largest of those 3rd generation synchrotron light sources are the European Synchrotron Radiation Facility (ESRF) in Grenoble, France, the Advanced Photon Source (APS) near Chicago, USA, and SPring-8 in Japan, accelerating electrons up to 6, 7 and 8 GeV, respectively.

Synchrotrons which are useful for cutting edge research are large machines, costing tens or hundreds of millions of dollars to construct, and each beamline (there may be 20 to 50 at a large synchrotron) costs another two or three million dollars on average. These installations are mostly built by the science funding agencies of governments of developed countries, or by collaborations between several countries in a region, and operated as infrastructure facilities available to scientists from universities and research organisations throughout the country, region, or world. More compact models, however, have been developed, such as the Compact Light Source.

List of installations

Synchrotron	Location & Country	Energy (GeV)	Circumference (m)	Commissioned	Decommissioned
Advanced Photon Source (APS)	Argonne National Laboratory, USA	7.0	1104	1995	
ALBA	Cerdanyola del Vallès near Barcelona, Spain	3	270	2010	
ISIS	Rutherford Appleton Laboratory, UK	0.8	163	1985	
Australian Synchrotron	Melbourne, Australia	3	216	2006	
ANKA	Karlsruhe Institute of Technology, Germany	2.5	110.4	2000	
LNLS	Campinas, Brazil	1.37	93.2	1997	
SESAME	Allaan, Jordan	2.5	125	Under Design	
Bevatron	Lawrence Berkeley Laboratory, USA	6	114	1954	1993
Advanced Light Source	Lawrence Berkeley Laboratory, USA	1.9	196.8	1993	
Cosmotron	Brookhaven National Laboratory, USA	3	72	1953	1968
National Synchrotron Light Source	Brookhaven National Laboratory, USA	2.8	170	1982	
Nimrod	Rutherford Appleton Laboratory, UK	7		1957	1978
Alternating Gradient Synchrotron (AGS)	Brookhaven National Laboratory, USA	33	800	1960	
Stanford Synchrotron Radiation Lightsource	SLAC National Accelerator Laboratory, USA	3	234	1973	
Synchrotron Radiation Center (SRC)	Madison, USA	1	121	1968	
Cornell High Energy Synchrotron Source (CHESS)	Cornell University, USA	5.5	768	1979	
Soleil	Paris, France	3	354	2006	
Shanghai Synchrotron Radiation Facility (SSRF)	Shanghai, China	3.5	432	2007	
Proton Synchrotron	CERN, Switzerland	28	628.3	1959	
Tevatron	Fermi National Accelerator Laboratory, USA	1000	6300	1983	
Swiss Light Source	Paul Scherrer Institute, Switzerland	2.8	288	2001	
Large Hadron Collider (LHC)	CERN, Switzerland	7000	26659	2008	
BESSY II	Helmholtz-Zentrum Berlin in Berlin, Germany	1.7	240	1998	
European Synchrotron Radiation Facility (ESRF)	Grenoble, France	6	844	1992	
MAX-I	MAX-lab, Sweden	0.55	30	1986	
MAX-II	MAX-lab, Sweden	1.5	90	1997	
MAX-III	MAX-lab, Sweden	0.7	36	2008	
ELETTRA	Trieste, Italy	2-2.4	260	1993	
Synchrotron Radiation Source	Daresbury Laboratory, UK	2	96	1980	2008

ASTRID	Aarhus University, Denmark	0.58	40	1991	
Diamond Light Source	Oxfordshire, UK	3	561.6	2006	
DORIS III	DESY, Germany	4.5	289	1980	
PETRA II	DESY, Germany	12	2304	1995	2007
PETRA III	DESY, Germany	6.5	2304	2009	
Canadian Light Source	University of Saskatchewan, Canada	2.9	171	2002	
SPring-8	RIKEN, Japan	8	1436	1997	
KEK	Tsukuba, Japan	12			
National Synchrotron Radiation Research Center	Hsinchu Science Park, Taiwan	3.3	518.4	2008	
Synchrotron Light Research Institute (SLRI)	Nakhon Ratchasima, Thailand	1.2	81.4	2004	
Indus 1	Raja Ramanna Centre for Advanced Technology, Indore, India	0.45		1999	
Indus 2	Raja Ramanna Centre for Advanced Technology, Indore, India	2.5	36	2005	
Synchrotron	JINR, Dubna, Russia	10	180	1957	2005
U-70 synchrotron	IHEP, Protvino, Russia	70		1967	
CAMD	LSU, Louisiana, US	1.5	-	-	
PLS	PAL, Pohang, Korea	2.5	280.56	1994	

- Note: in the case of colliders, the quoted energy is often double what is shown here. The above table shows the energy of one beam but if two opposing beams collide head on, the centre of mass energy is double the beam energy shown.

Applications

- Life sciences: protein and large molecule crystallography
- LIGA based microfabrication
- Drug discovery and research
- "Burning" computer chip designs into metal wafers
- Studying molecule shapes and protein crystals
- Analysing chemicals to determine their composition
- Observing the reaction of living cells to drugs
- Inorganic material crystallography and microanalysis
- Fluorescence studies
- Semiconductor material analysis and structural studies
- Geological material analysis
- Medical imaging
- Proton therapy to treat some forms of cancer

See also

- List of synchrotron radiation facilities
- Synchrotron X-ray tomographic microscopy
- Energy amplifier
- Superconducting Radio Frequency

References

- [1] Nature 407, 468 (28 September 2000) (<http://www.nature.com/nature/journal/v407/n6803/full/407468a0.html>).
- [2] The Cosmotron (<http://www.bnl.gov/bnlweb/history/cosmotron.asp>)

External links

- Canadian Light Source (<http://www.lightsource.ca>)
- Australian Synchrotron (<http://www.synchrotron.org.au>)
- Diamond UK Synchrotron (<http://www.diamond.ac.uk>)
- Lightsources.org (<http://www.lightsources.org/cms/>)
- CERN Large Hadron Collider (<http://lhc-new-homepage.web.cern.ch/lhc-new-homepage>)
- Synchrotron Light Sources of the World (http://www-als.lbl.gov/als/synchrotron_sources.html)
- A Miniature Synchrotron: (<http://www.technologyreview.com/Biotech/20149/>) room-size synchrotron offers scientists a new way to perform high-quality x-ray experiments in their own labs, *Technology Review*, February 04, 2008
- Brazilian Synchrotron Light Laboratory (http://www.lnls.br/lnls/cgi/cgilua.exe/sys/start.htm?UserActiveTemplate=lnls_2007_english&tpl=home)
- Podcast interview (<http://omegataupodcast.net/2009/03/28/11-synchrotron-radiation-science-at-esrf/>) with a scientist at the European Synchrotron Radiation Facility

Medical Diagnostics in Cardiology

Cardiology

Cardiologist

Occupation	
Names	Doctor, Medical Specialist
Type	Specialty
Activity sectors	Medicine
Description	
Education required	Doctor of Medicine
Fields of employment	Hospitals, Clinics

Cardiology (from Greek καρδίᾱ, *kardiā*, "heart"; and -λογία, *-logia*) is a medical specialty dealing with disorders of the heart. The field includes diagnosis and treatment of congenital heart defects, coronary artery disease, heart failure, valvular heart disease and electrophysiology. Physicians specializing in this field of medicine are called **cardiologists**. Cardiologists should not be confused with cardiac surgeons, cardiothoracic and cardiovascular, who are surgeons who perform cardiac surgery via sternotomy - open operative procedures on the heart and great vessels. The term *cardiology* is derived from the Greek word καρδιά (transliterated as *kardia* and meaning *heart* or *inner self*).

The Cardiac Muscle

Cardiac pacemaker (Electrical system of the heart)

- Electrical conduction system of the heart
 - Action potential
 - Ventricular action potential
- Sinoatrial node
- Atrioventricular node
- Bundle of His
- Purkinje fibers
- Heart Attack (Myocardial Infarction)

Basic cardiac physiology

- Systole
- Diastole
- Heart sounds
- Preload
- Afterload
- Kussmaul's signature

Disorders of the coronary circulation

- Atherosclerosis
- Restenosis
- Coronary heart disease (Ischaemic heart disease, Coronary artery disease)
- Acute coronary syndrome
 - Angina
 - Myocardial infarction (Heart attack)

Cardiac arrest

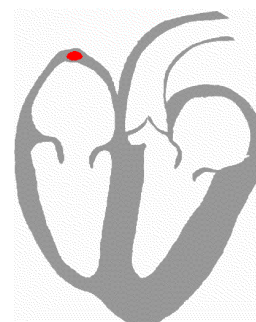
- Ventricular fibrillation
- Pulseless ventricular tachycardia
- Pulseless electrical activity
- Asystole
- Sudden cardiac death (The abrupt reduction or cessation of blood flow to the myocardium, leading to death)

Treatment of cardiac arrest

- Cardiopulmonary resuscitation (CPR)

Disorders of the myocardium (muscle of the heart)

- Cardiomyopathy
 - Ischemic cardiomyopathy
 - Nonischemic cardiomyopathy
 - Amyloid cardiomyopathy
 - Hypertrophic cardiomyopathy (HCM)
 - Hypertrophic obstructive cardiomyopathy (HOCM) (Idiopathic hypertrophic subaortic stenosis (IHSS))
 - hypertrophic cardiomyopathy
 - Dilated cardiomyopathy
 - Alcoholic cardiomyopathy
 - Tachycardia induced cardiomyopathy
 - Takotsubo cardiomyopathy (Transient apical ballooning, stress-induced cardiomyopathy)
 - Arrhythmogenic right ventricular dysplasia (Arrhythmogenic right ventricular cardiomyopathy)
 - Restrictive cardiomyopathy
- Congestive heart failure
 - Cor pulmonale



A diagram of a heart with an ECG indicator; diagrams like this are used in Cardiology.

- Ventricular hypertrophy
 - Left ventricular hypertrophy
 - Right ventricular hypertrophy
- Primary tumors of the heart
 - Myxoma
- Myocardial rupture

Disorders of the pericardium (outer lining of the heart)

- Pericarditis
- Pericardial tamponade
- Constrictive pericarditis

Disorders of the heart valves

- Aortic valve disorders and treatments:
 - Aortic insufficiency
 - Aortic stenosis
 - Aortic valve replacement
 - Aortic valve repair
 - Aortic valvuloplasty
- Mitral valve disorders and treatments:
 - Mitral valve prolapse
 - Mitral regurgitation
 - Mitral stenosis
 - Mitral valve replacement
 - Mitral valve repair
 - Mitral valvuloplasty
- Pulmonary valve disorders:
 - Congenital pulmonic stenosis
- Tricuspid valve disorders
 - Wolff-Parkinson-White syndrome (WPW syndrome)

Congenital heart disease

- Atrial septal defect
 - Ventricular septal defect
 - Patent ductus arteriosus
 - Bicuspid aortic valve
 - Tetralogy of Fallot
 - Transposition of the great vessels (TGV)
 - Hypoplastic left heart syndrome
 - Truncus Arteriosus
-

Diseases of blood vessels (Vascular diseases)

- Vasculitis
- Atherosclerosis
- Aneurysm
- Varicose veins
- Economy class syndrome
- Diseases of the aorta
 - Coarctation of the aorta
 - Aortic dissection
 - Aortic aneurysm
- Diseases of the carotid arteries
 - Carotid artery disease
 - Carotid artery dissection

Procedures done for coronary artery disease

- Percutaneous coronary intervention
 - Atherectomy
 - Angioplasty (PTCA)
 - Stenting
- Coronary artery bypass surgery (CABG)
- Enhanced external counterpulsation (EECP)

Devices used in cardiology

- Stethoscope
- Devices used to maintain normal electrical rhythm
 - Pacemaker
 - Defibrillator
 - Automated external defibrillator
 - Implantable cardioverter-defibrillator
- Devices used to maintain blood pressure
 - Artificial heart
 - Heart-lung machine
 - Intra-aortic balloon pump
 - Ventricular assist device

Diagnostic tests and procedures

- Blood tests
- Echocardiogram
- Cardiovascular Magnetic Resonance
- Cardiac stress test
- Auscultation (Listening with the Stethoscope)

Electrocardiogram (ECG or EKG)

- QT interval
- Osborn wave
- Ambulatory Holter monitor
- Electrophysiology study
 - Programmed electrical stimulation
- Sphygmomanometer (Blood pressure cuff)
- Cardiac enzymes
- Coronary catheterization
 - Myocardial Fractional Flow Reserve (FFRmyo)
 - IVUS (IntraVascular UltraSound)
 - OCT (Optical Coherence Tomography)

See also

- Interventional cardiology
- Clinical cardiac electrophysiology
- American Heart Association
- National Heart Foundation of Australia
- List of cardiac pharmaceutical agents

External links

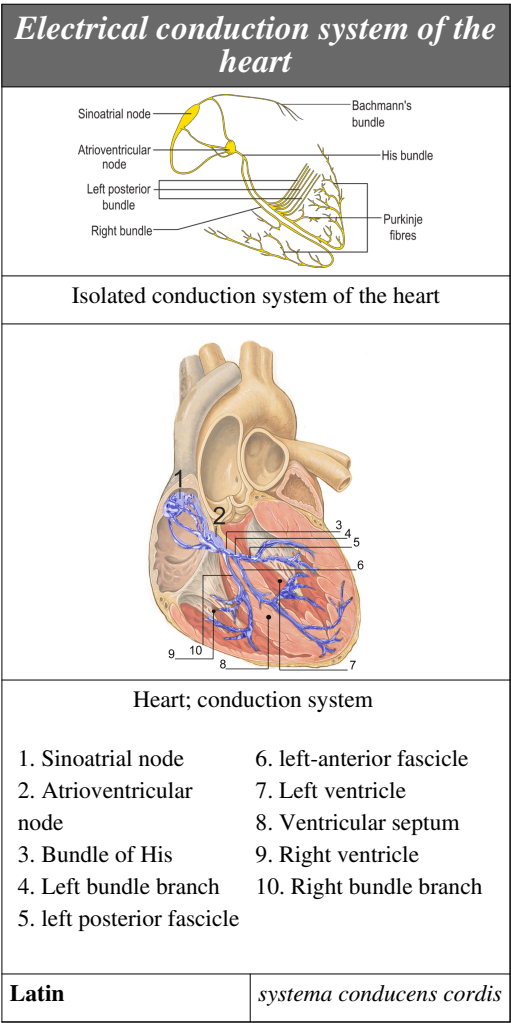
- U.S. National Institute of Health (NIH) : Heart and Circulation ^[1]
- American College of Cardiology ^[2]

References

[1] <http://health.nih.gov/search.asp/10>

[2] <http://www.acc.org>

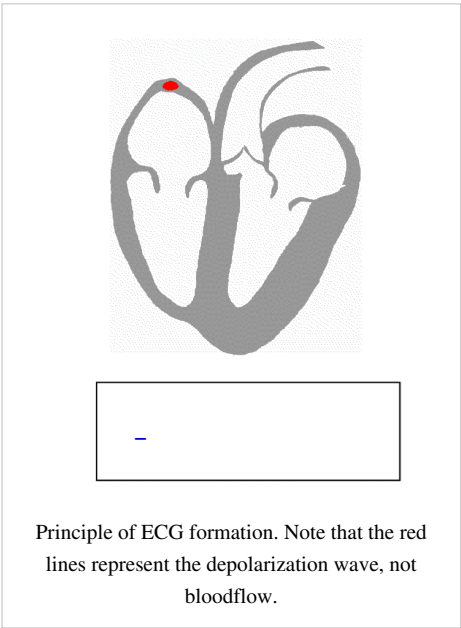
Electrical conduction system of the heart



The normal electrical conduction of the heart allows electrical propagation to be transmitted from the Sinoatrial Node through both atria and forward to the Atrioventricular Node. Normal/baseline physiology allows further propagation from the AV node to the Ventricle or Purkinje Fibers and respective bundle branches and subdivisions/fascicles. Both the SA and AV nodes stimulate the Myocardium. Time ordered stimulation of the myocardium allows efficient contraction of all four chambers of the heart, thereby allowing selective blood perfusion through both the lungs and systemic circulation.

Electrochemical mechanism

The neurons that innervate cardiac muscle hold some similarities to those of skeletal muscle as well as other important differences. These neurons are uniquely subject to influence by the sympathetic part of the autonomic nervous system.



Like a neuron, a given myocardial cell has a negative membrane potential when at rest. Stimulation above a threshold value induces the opening of voltage-gated ion channels and a flood of cations into the cell. The positively charged ions entering the cell cause the depolarization characteristic of an action potential. After depolarization, there's a brief repolarization that takes place with the efflux of potassium through fast acting potassium channels. Like skeletal muscle, depolarization causes the opening of voltage-gated calcium channels - meanwhile potassium channels have closed - and are followed by a titrated release of Ca^{2+} from the t-tubules. This influx of calcium causes calcium-induced calcium release from the sarcoplasmic reticulum, and free Ca^{2+} causes muscle contraction. After a delay, slow acting Potassium channels reopen and the resulting flow of K^{+} out of the cell causes repolarization to the resting state.

Note that there are important physiological differences between nodal cells and ventricular cells; the specific differences in ion channels and mechanisms of polarization give rise to unique properties of SA node cells, most importantly the spontaneous depolarizations necessary for the SA node's pacemaker activity.

Conduction pathway

Signals arising in the SA node (and propagating to the left atrium via Bachmann's bundle) stimulate the atria to contract. In parallel, action potentials travel to the AV node via internodal pathways. After a delay, the stimulus is conducted through the bundle of His to the bundle branches and then to the purkinje fibers and the endocardium at the apex of the heart, then finally to the ventricular myocardium.

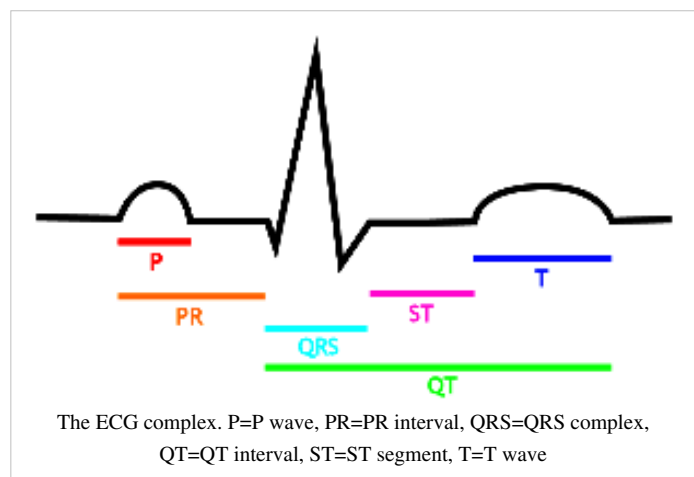
Microscopically, the wave of depolarization propagates to adjacent cells via gap junctions located on the intercalated disk. The heart is a *functional syncytium* (not to be confused with a true "syncytium" in which all the cells are fused together, sharing the same plasma membrane as in skeletal muscle). In a functional syncytium, electrical impulses propagate freely between cells in every direction, so that the myocardium functions as a single contractile unit. This property allows rapid, synchronous depolarization of the myocardium. While normally advantageous, this property can be detrimental as it potentially allows the propagation of incorrect electrical signals. These gap junctions can close to isolate damaged or dying tissue, as in a myocardial infarction.

Depolarization and the ECG

SA node: P wave

Under normal conditions, electrical activity is spontaneously generated by the SA node, the physiological pacemaker. This electrical impulse is propagated throughout the right atrium, and through Bachmann's bundle to the left atrium, stimulating the myocardium of both atria to contract. The conduction of the electrical impulse throughout the left and right atria is seen on the ECG as the **P wave**.

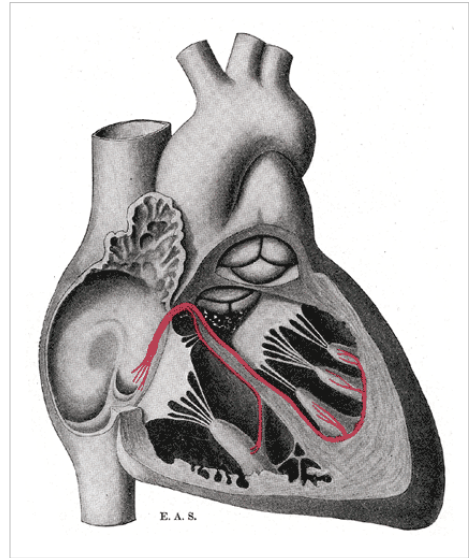
As the electrical activity is spreading throughout the atria, it travels via specialized pathways, known as *internodal tracts*, from the SA node to the AV node.



AV node/Bundles: PR interval

The AV node functions as a critical delay in the conduction system. Without this delay, the atria and ventricles would contract at the same time, and blood wouldn't flow effectively from the atria to the ventricles. The delay in the AV node forms much of the **PR segment** on the ECG. Part of atrial repolarization can be represented by PR segment.

The distal portion of the AV node is known as the bundle of His. The bundle of His splits into two branches in the interventricular septum, the left bundle branch and the right bundle branch. The left bundle branch activates the left ventricle, while the right bundle branch activates the right ventricle. The left bundle branch is short, splitting into the left anterior fascicle and the left posterior fascicle. The left posterior fascicle is relatively short and broad, with dual blood supply, making it particularly resistant to ischemic damage. The left posterior fascicle transmits impulses to the papillary muscles, leading to mitral valve closure. As the left posterior fascicle is shorter and broader than the right, impulses reach the papillary muscles just prior to depolarization, and therefore contraction, of the left ventricle myocardium. This allows pre-tensioning of the chordae tendinae, increasing the resistance to flow through the mitral valve during left ventricular contraction.



Purkinje fibers/ventricular myocardium: QRS complex

The two bundle branches taper out to produce numerous Purkinje fibers, which stimulate individual groups of myocardial cells to contract.

The spread of electrical activity (depolarization) through the ventricular myocardium produces the QRS complex on the ECG.

Ventricular repolarization: T wave

The last event of the cycle is the repolarization of the ventricles. The transthoracically measured PQRS portion of an electrocardiogram is chiefly influenced by the sympathetic nervous system. The T (and occasionally U) waves are chiefly influenced by the parasympathetic nervous system guided by integrated brainstem control from the vagus nerve and the thoracic spinal accessory ganglia.

Pathology

An impulse (action potential) that originates from the SA node at a relative rate of 60 - 100bpm is known as *normal sinus rhythm*. If SA nodal impulses occur at a rate less than 60bpm, the heart rhythm is known as sinus bradycardia. If SA nodal impulses occur at a rate exceeding 100bpm, the consequent rapid heart rate is sinus tachycardia. These conditions are not necessarily bad symptoms, however. Trained athletes, for example, usually show heart rates slower than 60bpm when not exercising. If the SA node fails to initialize, the AV junction can take over as the main pacemaker of the heart. The AV junction "surrounds" the AV node and has a regular rate of 40 to 60bpm. These "junctional" rhythms are characterized by a missing or inverted P-Wave. If both the SA node and the AV junction fail to initialize the electrical impulse, the ventricles can fire the electrical impulses themselves at a rate of 20 to 40bpm and will have a QRS complex of greater than 120ms.

Embryologic evidence

Embryologic evidence of generation of the cardiac conduction system illuminates the respective roles of this specialized set of cells. Innervation of the heart begins with a brain only centered parasympathetic cholinergic first order. It is then followed by rapid growth of a second order sympathetic adrenergic system arising from the formation of the Thoracic Spinal Ganglia. The third order of electrical influence of the heart is derived from the Vagus Nerve as the other peripheral organs form.^[1]

See also

- Bradycardia
- Cardiac pacemaker
- Electrocardiogram (ECG)
- Tachycardia
- Circle map – simplified mathematical model of the beating heart.

References

- [1] "Innervation of the heart" (<http://www.embryology.ch/anglais/pcardio/funktion02.html>). *Human Embryology: Organogenesis: Functional development of the heart*. .

External links

- Conduction system of the heart (http://www.mercksource.com/pp/us/cns/cns_hl_adam.jspzQzpgzEzzSzppdocszSzuszSzcnaszSzcontentzSzadamzSzimagepageszSz18052zPzhtm) - Merck Source

Coronary disease

Coronary disease	
<i>Classification and external resources</i>	
ICD-9	414.00
MeSH	D003327 ^[1]

Coronary disease (or **coronary heart disease**) refers to the failure of coronary circulation to supply adequate circulation to cardiac muscle and surrounding tissue. It is already the most common form of disease affecting the heart and an important cause of premature death in Europe, the Baltic states, Russia, North and South America, Australia and New Zealand. It has been predicted that all regions of the world will be affected by 2020.^[2]

It is most commonly equated with atherosclerotic coronary artery disease, but coronary disease can be due to other causes, such as coronary vasospasm.^[3] It is possible for the stenosis to be caused by the spasm.^[4]

Signs and symptoms

Coronary heart disease may be asymptomatic. If not, symptoms can include:

- Chest heaviness
- Dyspnea
- Fatigue
- Chest pain
- Angina'

Myocardial infarction is a complication of coronary disease. It is sometimes classified as a symptom.^{[5] [6]}

Causes

Coronary artery disease, the most common type of coronary disease, which has no clear etiology, has many risk factors, including smoking, radiotherapy to the chest, hypertension, diabetes, and hyperlipidemia.^[7]

Also, having a Type A behavior pattern, a group of personality characteristics including time urgency and competitiveness, is linked to an increased risk of coronary disease.^[8]

Treatment

Lifestyle changes

Lifestyle changes that may be useful in coronary disease include.

- Weight control
- Smoking cessation
- Exercise
- Healthy diet^[9] Over the past 50 years, doctors have recommended the reduction of animal based foods and an increase in plant based foods.^[10] However, many doctors have argued that it is an excess of carbohydrates, not animal fats^{[11] [12] [13]}, which cause coronary heart disease and have recommended eating more animal fat.

Medications to treat coronary disease

- Cholesterol lowering medications, such as statins, are useful to decrease the amount of "bad" (LDL) cholesterol.
- Nitroglycerin
- ACE inhibitors, which treat hypertension and may lower the risk of recurrent myocardial infarction
- Calcium channel blockers and/or beta-blockers
- Aspirin^[9]

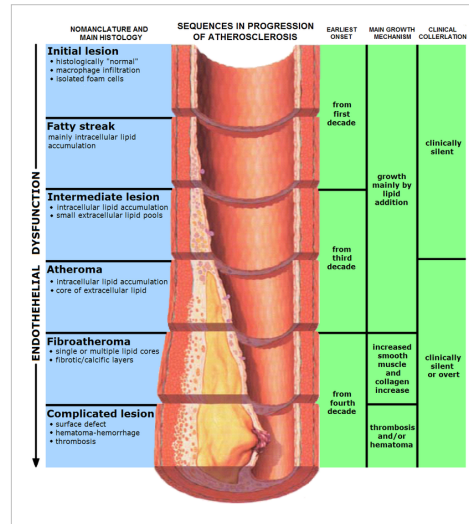
Surgical intervention

- Angioplasty
- Stents (bare-metal or drug-eluting)
- Coronary artery bypass^[9]
- Heart Transplant

References

- [1] http://www.nlm.nih.gov/cgi/mesh/2010/MB_cgi?field=uid&term=D003327
- [2] Boon NA, Colledge NR, Walker BR and Hunter JAA (2006). Davidson's Principles & Practice of Medicine, 20th Edition. Churchill Livingstone
- [3] Williams MJ, Restieaux NJ, Low CJ (February 1998). "Myocardial infarction in young people with normal coronary arteries" (<http://heart.bmj.com/cgi/lookup?view=long&pmid=9538315>). *Heart* **79** (2): 191–4. PMID 9538315. PMC 1728590. .
- [4] Rezkalla SH, Kloner RA (October 2007). "Cocaine-induced acute myocardial infarction" (<http://www.clinmedres.org/cgi/lookup?view=long&pmid=18056026>). *Clin Med Res* **5** (3): 172–6. doi:10.3121/cmr.2007.759. PMID 18056026. PMC 2111405. .
- [5] <https://health.google.com/health/ref/Coronary+heart+disease>
- [6] <http://www.mayoclinic.com/health/coronary-artery-disease/DS00064/DSECTION=symptoms>
- [7] <http://www.mayoclinic.com/health/coronary-artery-disease/DS00064/DSECTION=causes>
- [8] McCann, 2001, the precocity-longevity hypothesis: earlier peaks in career achievement predict shorter lives. *Personality & Social psychology bulletin*, 27, 1429-1439; Rhodewalt & Smith, 1991, current issues in Type A behaviour, coronary proneness, and coronary heart disease. In C.R. Snyder & D.R.Forsyth (Eds.), *Handbook of social and clinical psychology* (pp.197-220) New York: Pergamon
- [9] <http://www.mayoclinic.com/health/coronary-artery-disease/DS00064/DSECTION=treatments%2Dand%2Ddrugs>
- [10] morrison l m "diet in coronary artherosclerosis" *JAMA* 173; 1960; p884-888
- [11] Mente A, de Koning L, Shannon HS, Anand SS "A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease." (<http://www.ncbi.nlm.nih.gov/pubmed/19364995>), *Population Health Research Institute, Hamilton, Canada*, April 13, 2009. "pdf" (<http://www.dscience.net/mente-aim-2009.pdf>)
- [12] Siri-Tarino PW, Sun Q, Hu FB, Krauss RM "Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease." (<http://www.ncbi.nlm.nih.gov/pubmed/20071648>), *Children's Hospital, Oakland Research Institute Oakland, CA, USA*, *Am J Clin Nutr.* 2010 Mar;91(3):535-46. Epub 2010 Jan 13.
- [13] "Fats and Fatty Acids in Human Nutrition" (<http://content.karger.com/ProdukteDB/produkte.asp?Aktion=ShowEachType&ProduktNr=251867>), Joint FAO/WHO Expert Consultation, Geneva, November 2008, "Free Online Access" (<http://content.karger.com/ProdukteDB/produkte.asp?Aktion=Ausgabe&Ausgabe=250361&ProduktNr=223977>)

Classification and external resources



ICD-10	I 70. ^[1]
ICD-9	440 ^[2] , 414.0 ^[3]
DiseasesDB	1039 ^[4]
MedlinePlus	000171 ^[5]
eMedicine	med/182 ^[6]
MeSH	D050197 ^[7]

The atheromatous plaque is divided into three distinct components:

- The following terms are similar, yet distinct, in both spelling and meaning, and can be easily confused: arteriosclerosis, arteriolosclerosis, and atherosclerosis. *Arteriosclerosis* is a general term describing any hardening (and loss of elasticity) of medium or large arteries (from the Greek *arteria*, meaning *artery*, and *sclerosis*, meaning *hardening*); *arteriolosclerosis* is any hardening (and loss of elasticity) of arterioles (small arteries); *atherosclerosis* is

a hardening of an artery specifically due to an atheromatous plaque. The term *atherogenic* is used for substances or processes that cause atherosclerosis.

Atherosclerosis, though typically asymptomatic for decades, eventually produces two main problems: First, the atheromatous plaques, though long compensated for by artery enlargement (see IMT), eventually lead to plaque ruptures and clots inside the artery lumen over the ruptures. The clots heal and usually shrink but leave behind stenosis (narrowing) of the artery (both locally and in smaller downstream branches), or worse, complete closure, and, therefore, an insufficient blood supply to the tissues and organ it feeds. Second, if the compensating artery enlargement process is excessive, then a net aneurysm results.

These complications of advanced atherosclerosis are chronic, slowly progressive and cumulative. Most commonly, soft plaque suddenly ruptures (see vulnerable plaque), causing the formation of a thrombus that will rapidly slow or stop blood flow, leading to death of the tissues fed by the artery in approximately 5 minutes. This catastrophic event is called an infarction. One of the most common recognized scenarios is called coronary thrombosis of a coronary artery, causing myocardial infarction (a heart attack). Even worse is the same process in an artery to the brain, commonly called stroke. Another common scenario in very advanced disease is claudication from insufficient blood supply to the legs, typically due to a combination of both stenosis and aneurysmal segments narrowed with clots. Since atherosclerosis is a body-wide process, similar events occur also in the arteries to the brain, intestines, kidneys, legs, etc. Many infarctions involve only very small amounts of tissue and are termed clinically silent, because the person having the infarction does not notice the problem, does not seek medical help or when they do, physicians do not recognize what has happened.

Signs and symptoms

Atherosclerosis typically begins in early adolescence, and is usually found in most major arteries, yet is asymptomatic and not detected by most diagnostic methods during life. Atheroma in arm, or more often in leg arteries, which produces decreased blood flow is called peripheral artery occlusive disease (PAOD).

According to United States data for the year 2004, for about 65% of men and 47% of women, the first symptom of atherosclerotic cardiovascular disease is heart attack or sudden cardiac death (death within one hour of onset of the symptom).

Most artery flow disrupting events occur at locations with *less* than 50% lumen narrowing (~20% stenosis is average). The illustration above, like most illustrations of arterial disease, overemphasizes lumen narrowing, as opposed to compensatory external diameter enlargement (at least within smaller arteries, e.g., heart arteries) typical of the atherosclerosis process as it progresses (see Glagov^[9] the ASTEROID trial,^[10] and the IVUS photographs on page 8, as examples for a more accurate understanding). The relative geometry error within the illustration is common to many older illustrations, an error slowly being more commonly recognized within the last decade.

Cardiac stress testing, traditionally the most commonly performed non-invasive testing method for blood flow limitations, in general, detects only lumen narrowing of ~75% or greater, although some physicians claim that nuclear stress methods can detect as little as 50%.

==Causes== (how it is formed) Atherosclerosis develops from low-density lipoprotein molecules (LDL) becoming oxidized (ldl-ox) by free radicals, particularly reactive oxygen species (ROS). When oxidized LDL comes in contact with an artery wall, a series of reactions occur to repair the damage to the artery wall caused by oxidized LDL. The LDL molecule is globular shaped with a hollow core to carry cholesterol throughout the body. Cholesterol can move in the bloodstream only by being transported by lipoproteins.

The body's immune system responds to the damage to the artery wall caused by oxidized LDL by sending specialized white blood cells (macrophages and T-lymphocytes) to absorb the oxidized-LDL forming specialized foam cells. These white blood cells are not able to process the oxidized-LDL, and ultimately grow then rupture, depositing a greater amount of oxidized cholesterol into the artery wall. This triggers more white blood cells,

continuing the cycle.

Eventually, the artery becomes inflamed. The cholesterol plaque causes the muscle cells to enlarge and form a hard cover over the affected area. This hard cover is what causes a narrowing of the artery, reduces the blood flow and increases blood pressure.

Some researchers believe that atherosclerosis may be caused by an infection of the vascular smooth muscle cells; chickens, for example, develop atherosclerosis when infected with the Marek's disease herpesvirus.^[11] Herpesvirus infection of arterial smooth muscle cells has been shown to cause cholesteryl ester (CE) accumulation.^[12] Cholesteryl ester accumulation is associated with atherosclerosis.

Also, cytomegalovirus (CMV) infection is associated with cardiovascular diseases.^[13]

Risk factors

Various anatomic, physiological and behavioral risk factors for atherosclerosis are known.^[14] These can be divided into various categories: congenital *vs* acquired, modifiable or not, classical or non-classical. The points labelled '+' in the following list form the core components of metabolic syndrome.

Risks multiply, with two factors increasing the risk of atherosclerosis fourfold.^[15] Hyperlipidemia, hypertension and cigarette smoking together increases the risk seven times.^[15]

Modifiable

- Diabetes^[15] or Impaired glucose tolerance (IGT) +
- Dyslipoproteinemia^[15] (unhealthy patterns of serum proteins carrying fats & cholesterol): +
 - High serum concentration of low-density lipoprotein (LDL, "bad if elevated concentrations and small"), and / or very low density lipoprotein (VLDL) particles, i.e., "lipoprotein subclass analysis"
 - Low serum concentration of functioning high density lipoprotein (HDL "protective if large and high enough" particles), i.e., "lipoprotein subclass analysis"
 - An LDL:HDL ratio greater than 3:1
- Tobacco smoking, increases risk by 200% after several pack years^[15]
- Having hypertension +, on its own increasing risk by 60%^[15]
- Elevated serum C-reactive protein concentrations^[15] [16]

Nonmodifiable

- Advanced age^[15]
- Male sex^[15]
- Having close relatives who have had some complication of atherosclerosis (e.g. coronary heart disease or stroke)^[15]
- Genetic abnormalities,^[15] e.g. familial hypercholesterolemia

Lesser or uncertain

The following factors are of relatively lesser importance, are uncertain or unquantified:

- Obesity^[15] (in particular central obesity, also referred to as *abdominal* or *male-type* obesity) +
- A sedentary lifestyle^[15]
- Postmenopausal estrogen deficiency^[15]
- High carbohydrate intake^[15]
- Intake of trans fat^[15]
- Elevated serum levels of triglycerides +
- Elevated serum levels of homocysteine
- Elevated serum levels of uric acid (also responsible for gout)
- Elevated serum fibrinogen concentrations
- Elevated serum lipoprotein(a) concentrations^[15]

- Chronic systemic inflammation as reflected by upper normal WBC concentrations, elevated hs-CRP and many other blood chemistry markers, most only research level at present, not clinically done.^[17]
- Stress^[15] or symptoms of clinical depression
- Hyperthyroidism (an over-active thyroid)
- Elevated serum insulin levels +^[18]
- Short sleep duration^[19]
- Chlamydia pneumoniae infection^[15]

Dietary (diet-meaning what you are eating)

The relation between dietary fat and atherosclerosis is a contentious field. The USDA, in its food pyramid, promotes a low-fat diet, based largely on its view that fat in the diet is atherogenic. The American Heart Association, the American Diabetes Association and the National Cholesterol Education Program make similar recommendations. In contrast, Prof Walter Willett (Harvard School of Public Health, PI of the second Nurses' Health Study) recommends much higher levels, especially of monounsaturated and polyunsaturated fat.^[20] Writing in *Science*, Gary Taubes detailed that political considerations played into the recommendations of government bodies.^[21] These differing views reach a consensus, though, against consumption of trans fats.

The role of dietary oxidized fats / lipid peroxidation (rancid fats) in humans is not clear. Laboratory animals fed rancid fats develop atherosclerosis. Rats fed DHA-containing oils experienced marked disruptions to their antioxidant systems, as well as accumulated significant amounts of peroxide in their blood, livers and kidneys.^[22] In another study, rabbits fed atherogenic diets containing various oils were found to undergo the greatest amount of oxidative susceptibility of LDL via polyunsaturated oils.^[23] In a study involving rabbits fed heated soybean oil, "grossly induced atherosclerosis and marked liver damage were histologically and clinically demonstrated."^[24]

Rancid fats and oils taste very bad even in small amounts; people avoid eating them.^[25] It is very difficult to measure or estimate the actual human consumption of these substances.^[26] In addition, the majority of oils consumed in the United States are refined, bleached, deodorized and degummed by manufacturers. The resultant oils are colorless, odorless, tasteless and have a longer shelf life than their unrefined counterparts.^[27] This extensive processing serves to make peroxidated, rancid oils much more elusive to detection via the various human senses than the unprocessed alternatives.

Pathophysiology

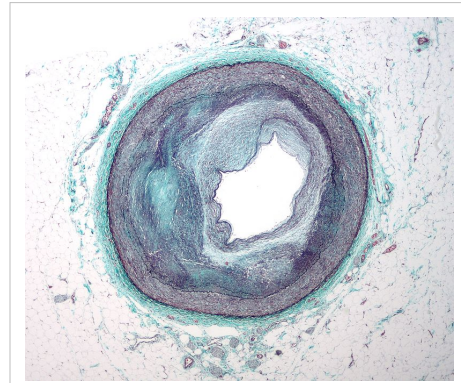
Atherogenesis is the developmental process of atheromatous plaques. It is characterized by a remodeling of arteries involving the concomitant accumulation of fatty substances called plaques. One recent theory suggests that, for unknown reasons, leukocytes, such as monocytes or basophils, begin to attack the endothelium of the artery lumen in cardiac muscle. The ensuing inflammation leads to formation of atheromatous plaques in the arterial tunica intima, a region of the vessel wall located between the endothelium and the tunica media. The bulk of these lesions is made of excess fat, collagen, and elastin. At first, as the plaques grow, only wall thickening occurs without any narrowing, stenosis of the artery opening, called the lumen; stenosis is a late event, which may never occur and is often the result of repeated plaque rupture and healing responses, not just the atherosclerosis process by itself.

Cellular

The first step of atherogenesis is the development of so called "fatty streaks," which are small sub-endothelial deposits of monocyte-derived macrophages. The primary documented driver of this process is oxidized Lipoprotein particles within the wall, beneath the endothelial cells, though upper normal or elevated concentrations of blood glucose also plays a major role and not all factors are fully understood. Fatty streaks may appear and disappear.

Low Density Lipoprotein particles in blood plasma, when they invade the endothelium and become oxidized creates a risk for cardiovascular disease. A complex set of biochemical reactions regulates the oxidation of LDL, chiefly stimulated by presence of enzymes, e.g. Lp-LpA2 and free radicals in the endothelium or blood vessel lining.

The initial damage to the blood vessel wall results in a "call for help," an inflammatory response. Monocytes (a type of white blood cell) enter the artery wall from the bloodstream, with platelets adhering to the area of insult. This may be promoted by redox signaling induction of factors such as VCAM-1, which recruit circulating monocytes. The monocytes differentiate macrophages, which ingest oxidized LDL, slowly turning into large "foam cells" – so-described because of their changed appearance resulting from the numerous internal cytoplasmic vesicles and resulting high lipid content. Under the microscope, the lesion now appears as a fatty streak. Foam cells eventually die, and further propagate the inflammatory process. There is also smooth muscle proliferation and migration from tunica media to intima responding to cytokines secreted by damaged endothelial cells. This would cause the formation of a fibrous capsule covering the fatty streak.



Micrograph of an artery that supplies the heart with significant atherosclerosis and marked luminal narrowing. Tissue has been stained using Masson's trichrome.

Calcification and lipids

Intracellular microcalcifications form within vascular smooth muscle cells of the surrounding muscular layer, specifically in the muscle cells adjacent to the atheromas. In time, as cells die, this leads to extracellular calcium deposits between the muscular wall and outer portion of the atheromatous plaques. A similar form of an intramural calcification, presenting the picture of an early phase of arteriosclerosis, appears to be induced by a number of drugs that have an antiproliferative mechanism of action (Rainer Liedtke 2008).

Cholesterol is delivered into the vessel wall by cholesterol-containing low-density lipoprotein (LDL) particles. To attract and stimulate macrophages, the cholesterol must be released from the LDL particles and oxidized, a key step in the ongoing inflammatory process. The process is worsened if there is insufficient high-density lipoprotein (HDL), the lipoprotein particle that removes cholesterol from tissues and carries it back to the liver.

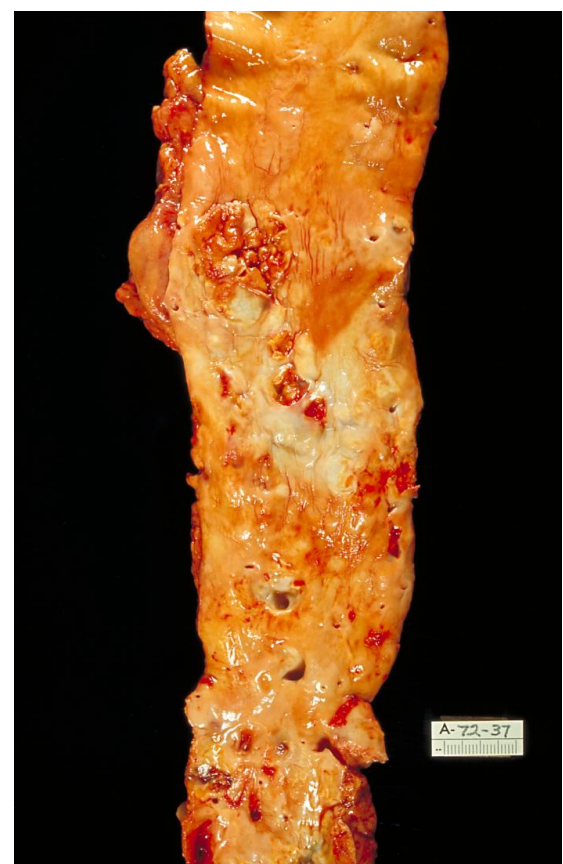
The foam cells and platelets encourage the migration and proliferation of smooth muscle cells, which in turn ingest lipids, become replaced by collagen and transform into foam cells themselves. A protective fibrous cap normally forms between the fatty deposits and the artery lining (the intima).

These capped fatty deposits (now called 'atheromas') produce enzymes that cause the artery to enlarge over time. As long as the artery enlarges sufficiently to compensate for the extra thickness of the atheroma, then no narrowing ("stenosis") of the opening ("lumen") occurs. The artery becomes expanded with an egg-shaped cross-section, still with a circular opening. If the enlargement is beyond proportion to the atheroma thickness, then an aneurysm is created.^[9]

Visible features

Although arteries are not typically studied microscopically, two plaque types can be distinguished.^[28]

1. The **fibro-lipid (fibro-fatty) plaque** is characterized by an accumulation of lipid-laden cells underneath the intima of the arteries, typically without narrowing the lumen due to compensatory expansion of the bounding muscular layer of the artery wall. Beneath the endothelium there is a "fibrous cap" covering the atheromatous "core" of the plaque. The core consists of lipid-laden cells (macrophages and smooth muscle cells) with elevated tissue cholesterol and cholesterol ester content, fibrin, proteoglycans, collagen, elastin, and cellular debris. In advanced plaques, the central core of the plaque usually contains extracellular cholesterol deposits (released from dead cells), which form areas of cholesterol crystals with empty, needle-like clefts. At the periphery of the plaque are younger "foamy" cells and capillaries. These plaques usually produce the most damage to the individual when they rupture.
2. The **fibrous plaque** is also localized under the intima, within the wall of the artery resulting in thickening and expansion of the wall and, sometimes, spotty localized narrowing of the lumen with some atrophy of the muscular layer. The fibrous plaque contains collagen fibers (eosinophilic), precipitates of calcium (hematoxylinophilic) and, rarely, lipid-laden cells.



Severe atherosclerosis of the aorta. Autopsy specimen.

In effect, the muscular portion of the artery wall forms small aneurysms just large enough to hold the atheroma that are present. The muscular portion of artery walls usually remain strong, even after they have remodeled to compensate for the atheromatous plaques.

However, atheromas within the vessel wall are soft and fragile with little elasticity. Arteries constantly expand and contract with each heartbeat, i.e., the pulse. In addition, the calcification deposits between the outer portion of the atheroma and the muscular wall, as they progress, lead to a loss of elasticity and stiffening of the artery as a whole.

The calcification deposits, after they have become sufficiently advanced, are partially visible on coronary artery computed tomography or electron beam tomography (EBT) as rings of increased radiographic density, forming halos around the outer edges of the atheromatous plaques, within the artery wall. On CT, >130 units on the Hounsfield scale (some argue for 90 units) has been the radiographic density usually accepted as clearly representing tissue calcification within arteries. These deposits demonstrate unequivocal evidence of the disease, relatively advanced, even though the lumen of the artery is often still normal by angiographic or intravascular ultrasound.

In days gone by the lateral chest x-ray (demonstrating greater opacity in the aortic arch and descending aorta than the thoracic spine) gave an indication to the degree of calcified plaque burden a patient had. This has been known as Piper's sign and can often be seen in elderly persons particularly those with concomitant osteoporosis.

Rupture and stenosis

Although the disease process tends to be slowly progressive over decades, it usually remains asymptomatic until an atheroma ulcerates, which leads to immediate blood clotting at the site of atheroma ulcer. This triggers a cascade of events that leads to clot enlargement, which may quickly obstruct the flow of blood. A complete blockage leads to ischemia of the myocardial (heart) muscle and damage. This process is the myocardial infarction or "heart attack."

If the heart attack is not fatal, fibrous organization of the clot within the lumen ensues, covering the rupture but also producing stenosis or closure of the lumen, or over time and after repeated ruptures, resulting in a persistent, usually localized stenosis or blockage of the artery lumen. Stenoses can be slowly progressive, whereas plaque ulceration is a sudden event that occurs specifically in atheromas with thinner/weaker fibrous caps that have become "unstable."

Repeated plaque ruptures, ones not resulting in total lumen closure, combined with the clot patch over the rupture and healing response to stabilize the clot, is the process that produces most stenoses over time. The stenotic areas tend to become more stable, despite increased flow velocities at these narrowings. Most major blood-flow-stopping events occur at large plaques, which, prior to their rupture, produced very little if any stenosis.

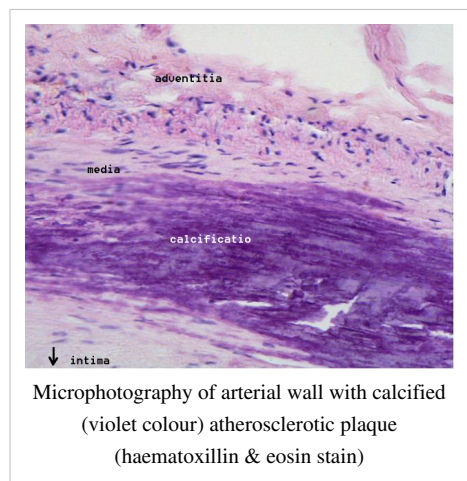
From clinical trials, 20% is the average stenosis at plaques that subsequently rupture with resulting complete artery closure. Most severe clinical events do not occur at plaques that produce high-grade stenosis. From clinical trials, only 14% of heart attacks occur from artery closure at plaques producing a 75% or greater stenosis prior to the vessel closing.

If the fibrous cap separating a soft atheroma from the bloodstream within the artery ruptures, tissue fragments are exposed and released, and blood enters the atheroma within the wall and sometimes results in a sudden expansion of the atheroma size. Tissue fragments are very clot-promoting, containing collagen and tissue factor; they activate platelets and activate the system of coagulation. The result is the formation of a thrombus (blood clot) overlying the atheroma, which obstructs blood flow acutely. With the obstruction of blood flow, downstream tissues are starved of oxygen and nutrients. If this is the myocardium (heart muscle), angina (cardiac chest pain) or myocardial infarction (heart attack) develops.

Diagnosis

Areas of severe narrowing, stenosis, detectable by angiography, and to a lesser extent "stress testing" have long been the focus of human diagnostic techniques for cardiovascular disease, in general. However, these methods focus on detecting only severe narrowing, not the underlying atherosclerosis disease. As demonstrated by human clinical studies, most severe events occur in locations with heavy plaque, yet little or no lumen narrowing present before debilitating events suddenly occur. Plaque rupture can lead to artery lumen occlusion within seconds to minutes, and potential permanent debility and sometimes sudden death.

Plaques that have ruptured are called complicated plaques. The lipid matrix breaks through the thinning collagen gap and when the lipids come in contact with the blood, clotting occurs. After rupture the platelet adhesion causes the clotting cascade to contact with the lipid pool causing a thrombus to form. This thrombus will eventually grow and travel throughout the body. The thrombus will travel through different arteries and veins and eventually become lodged in an area that narrows. Once the area is blocked, blood and oxygen will not be able to supply the vessels and will cause death of cells and lead to necrosis and poisoning. Serious complicated plaques can cause death of organ tissues, causing serious complications to that organ system.



Greater than 75% lumen stenosis used to be considered by cardiologists as the hallmark of clinically significant disease because it is typically only at this severity of narrowing of the larger heart arteries that recurring episodes of angina and detectable abnormalities by stress testing methods are seen. However, clinical trials have shown that only about 14% of clinically-debilitating events occur at locations with this, or greater severity of stenosis. The majority of events occur due to atheroma plaque rupture at areas without narrowing sufficient enough to produce any angina or stress test abnormalities. Thus, since the later-1990s, greater attention is being focused on the "vulnerable plaque."^[29]

Though any artery in the body can be involved, usually only severe narrowing or obstruction of some arteries, those that supply more critically-important organs are recognized. Obstruction of arteries supplying the heart muscle result in a heart attack. Obstruction of arteries supplying the brain result in a stroke. These events are life-changing, and often result in irreversible loss of function because lost heart muscle and brain cells do not grow back to any significant extent, typically less than 2%.

Over the last couple of decades, methods other than angiography and stress-testing have been increasingly developed as ways to better detect atherosclerotic disease before it becomes symptomatic. These have included both (a) anatomic detection methods and (b) physiologic measurement methods.

Examples of anatomic methods include: (1) coronary calcium scoring by CT, (2) carotid IMT (intimal media thickness) measurement by ultrasound, and (3) IVUS.

Examples of physiologic methods include: (1) lipoprotein subclass analysis, (2) HbA1c, (3) hs-CRP, and (4) homocysteine.

The example of the metabolic syndrome combines both anatomic (abdominal girth) and physiologic (blood pressure, elevated blood glucose) methods.

Advantages of these two approaches: The anatomic methods directly measure some aspect of the actual atherosclerotic disease process itself, thus offer potential for earlier detection, including before symptoms start, disease staging and tracking of disease progression. The physiologic methods are often less expensive and safer and changing them for the better may slow disease progression, in some cases with marked improvement.

Disadvantages of these two approaches: The anatomic methods are generally more expensive and several are invasive, such as IVUS. The physiologic methods do not quantify the current state of the disease or directly track progression. For both, clinicians and third party payers have been slow to accept the usefulness of these newer approaches.

Treatment

If atherosclerosis leads to symptoms, some symptoms such as angina pectoris can be treated. Non-pharmaceutical means are usually the first method of treatment, such as cessation of smoking and practicing regular exercise. If these methods do not work, medicines are usually the next step in treating cardiovascular diseases, and, with improvements, have increasingly become the most effective method over the long term. However, medicines are criticized for their expense, patented control and occasional undesired effects.

Statins

In general, the group of medications referred to as statins has been the most popular and are widely prescribed for treating atherosclerosis. They have relatively few short-term or longer-term undesirable side-effects, and multiple comparative treatment/placebo trials have fairly consistently shown strong effects in reducing atherosclerotic disease 'events' and generally ~25% comparative mortality reduction in clinical trials, although one study design, ALLHAT,^[30] was less strongly favorable.

The newest statin, rosuvastatin, has been the first to demonstrate regression of atherosclerotic plaque within the coronary arteries by IVUS (intravascular ultrasound evaluation).^[10] The study was set up to demonstrate effect

primarily on atherosclerosis volume within a 2 year time-frame in people with active/symptomatic disease (angina frequency also declined markedly) but not global clinical outcomes, which was expected to require longer trial time periods; these longer trials remain in progress.

However, for most people, changing their physiologic behaviors, from the usual high risk to greatly reduced risk, requires a combination of several compounds, taken on a daily basis and indefinitely. More and more human treatment trials have been done and are ongoing that demonstrate improved outcome for those people using more-complex and effective treatment regimens that change physiologic behaviour patterns to more closely resemble those that humans exhibit in childhood at a time before fatty streaks begin forming.

The statins, and some other medications, have been shown to have antioxidant effects, possibly part of their basis for some of their therapeutic success in reducing cardiac 'events'.

The success of statin drugs in clinical trials is based on some reductions in mortality rates, however by trial design biased toward men and middle-age, the data is as, as yet, less strongly clear for women and people over the age of 70.^[31] For example, in the Scandinavian Simvastatin Survival Study (4S), the first large placebo controlled, randomized clinical trial of a statin in people with advanced disease who had already suffered a heart attack, the overall mortality rate reduction for those taking the statin, vs. placebo, was 30%. For the subgroup of people in the trial that had Diabetes Mellitus, the mortality rate reduction between statin and placebo was 54%. 4S was a 5.4-year trial that started in 1989 and was published in 1995 after completion. There were 3 more dead women at trial's end on statin than in the group on placebo drug whether chance or some relation to the statin remains unclear. The ASTEROID trial has been the first to show actual disease volume regression^[10] (see page 8 of the paper, which shows cross-sectional areas of the total heart artery wall at start and 2 years of rosuvastatin 40 mg/day treatment); however, its design was not able to "prove" the mortality reduction issue since it did not include a placebo group, the individuals offered treatment within the trial had advanced disease and promoting a comparison placebo arm was judged to be unethical.

Primary and secondary prevention

Combinations of statins, niacin, intestinal cholesterol absorption-inhibiting supplements (ezetimibe and others, and to a much lesser extent fibrates) have been the most successful in changing common but sub-optimal lipoprotein patterns and group outcomes. In the many secondary prevention and several primary prevention trials, several classes of lipoprotein-expression-altering (less correctly termed "cholesterol-lowering") agents have consistently reduced not only heart attack, stroke and hospitalization but also all-cause mortality rates. The first of the large secondary prevention comparative statin/placebo treatment trials was the Scandinavian Simvastatin Survival Study (4S)^[32] with over fifteen more studies extending through to the more recent ASTEROID^[33] trial published in 2006. The first primary prevention comparative treatment trial was AFCAPS/TexCAPS^[34] with multiple later comparative statin/placebo treatment trials including EXCEL,^[35] ASCOT^[36] and SPARCL.^[37] ^[38] While the statin trials have all been clearly favorable for improved human outcomes, only ASTEROID showed evidence of atherosclerotic regression (slight). Both human and animal trials that showed evidence of disease regression used more aggressive combination agent treatment strategies, which nearly always included niacin.^[14]

Diet and dietary supplements

Niacin (vitamin B₃), in pharmacologic doses, (generally 1,000 to 3,000 mg/day), sold in many OTC and prescription formulations, tends to improve (a) HDL levels, size and function, (b) shift LDL particle distribution to larger particle size and (c) lower lipoprotein(a), an atherosclerosis promoting genetic variant of LDL. Additionally, individual responses to daily niacin, while mostly evident after a month at effective doses, tends to continue to slowly improve further over time. (However, careful patient understanding of how to achieve this without nuisance symptoms is needed, though not often achieved.) Research work on increasing HDL particle concentration and function, beyond the usual niacin effect/response, even more important, is slowly advancing.

Dietary changes to achieve benefit have been more controversial, generally far less effective and less widely adhered to with success. One key reason for this is that most cholesterol, typically 80-90%, within the body is created and controlled by internal production by all cells in the body (true of all animals), with typically slightly greater relative production by hepatic/liver cells. (Cell structure relies on fat membranes to separate and organize intracellular water, proteins and nucleic acids and cholesterol is one of the components of all animal cell membranes.)

While the absolute production quantities vary with the individual, group averages for total human body content of cholesterol within the U.S. population commonly run about 35,000 mg (assuming lean build; varies with body weight and build) and about 1,000 mg/day ongoing production. Dietary intake plays a smaller role, 200–300 mg/day being common values; for pure vegetarians, essentially 0 mg/day, but this typically does not change the situation very much because internal production increases to largely compensate for the reduced intake. For many, especially those with greater than optimal body mass and increased glucose levels, reducing carbohydrate (especially simple forms) intake, not fats or cholesterol, is often more effective for improving lipoprotein expression patterns, weight and blood glucose values. For this reason, medical authorities much less frequently promote the low dietary fat concepts than was commonly the case prior to about year 2005. However, evidence has increased that processed, particularly industrial non-enzymatic hydrogenation produced trans fats, as opposed to the natural cis-configured fats, which living cells primarily produce, is a significant health hazard.

Dietary supplements of Omega-3 oils, especially those from the muscle of some deep salt water living fish species, also have clinical evidence of significant protective effects as confirmed by 6 double blind placebo controlled human clinical trials.

Less robust evidence shows that homocysteine and uric acid levels, including within the normal range, promote atherosclerosis and that lowering these levels is helpful.

In animals Vitamin C deficiency has been confirmed as an important role in development of hypercholesterolemia and atherosclerosis, but due to ethical reasons placebo-controlled human studies are impossible to do.^[39] Vitamin C acts as an antioxidant in vessels and inhibits inflammatory process.^[40] It has therapeutic properties on high blood pressure and its fluctuation,^{[41] [42]} and arterial stiffness in diabetes.^[43] Vitamin C is also a natural regulator of cholesterol^[44] and higher doses (over 150 mg/kg daily) may confer significant protection against atherosclerosis even in the situation of elevated cholesterol levels.^{[45] [46]}

The scale of vitamin C benefits on cardiovascular system led several authors to theorize that vitamin C deficiency is the primary cause of cardiovascular diseases.^[47] The theory was unified by twice Nobel prize winner Linus Pauling and Matthias Rath. They point out that vitamin C is produced by all mammals except mankind and the great apes. This is due to a genetic deficiency that arose with the common ancestor of human and apes. To survive humans and apes must eat sufficient vitamin C each day. Without vitamin C humans develop scurvy. Vitamin C is an essential element in insuring that the vascular system is strong and flexible. Pauling and Matthias suggest that a deficiency causes weakness in the arterial system and the body compensates by trying to stiffen up the artery walls using other common blood elements. This causes the effect known as atherosclerosis. They suggest that clinical manifestations of cardiovascular diseases are merely overshoot of body defense mechanisms that are involved in stabilisation of vascular wall after it is weakened by the vitamin C deficiency and the subsequent collagen degradation. They discuss several metabolic and genetic predispositions (our inability to produce vitamin C at all being the main one) and their pathomechanism.^[48]

The Unified Theory of Human Cardiovascular Disease suggests that atherosclerosis may be reversed and cured but no testing or trials have yet been started to test Pauling's vitamin C theory.

Trials on Vitamin E have been done, but they have failed to find a beneficial effect, for various reasons, but for some patients at high risk for atherosclerosis there may be some benefits.^[49]

Menaquinone (Vitamin K₂), but not phylloquinone (Vitamin K₁), intake is associated with reduced risk of CHD mortality, all-cause mortality and severe aortic calcification.^{[50] [51] [52]}

Excess iron may be involved in the development of atherosclerosis,^{[53] [54]} but one study found reducing body iron stores in patients with symptomatic peripheral artery disease through phlebotomy did not significantly decrease all-cause mortality or death plus nonfatal myocardial infarction and stroke.^[55] Further studies may be warranted.

Changes in diet may help prevent the development of atherosclerosis. Researchers at the Agricultural Research Service have found that avenanthramides, chemical compounds found in oats, may help reduce the inflammation of the arterial wall, which contributes to the development of atherosclerosis. Avenanthramides have anti-inflammatory properties that are linked to activating proinflammatory cytokines. Cytokines are proteins that are released by the cell to protect and repair tissues. Researchers found that these compounds in oats have the ability to reduce inflammation and therefore help prevent atherosclerosis. [56]

Surgical intervention

Other physical treatments, helpful in the short term, include minimally invasive angioplasty procedures that may include stents to physically expand narrowed arteries^[57] and major invasive surgery, such as bypass surgery, to create additional blood supply connections that go around the more severely narrowed areas.

Prophylaxis

Patients at risk for atherosclerosis-related diseases are increasingly being treated prophylactically with low-dose aspirin and a statin. The high incidence of cardiovascular disease led Wald and Law^[58] to propose a *Polypill*, a once-daily pill containing these two types of drugs in addition to an ACE inhibitor, diuretic, beta blocker, and folic acid. They maintain that high uptake by the general population by such a *Polypill* would reduce cardiovascular mortality by 80%. It must be emphasized however that this is purely theoretical, as the *Polypill* has never been tested in a clinical trial.

Medical treatments often focus predominantly on the symptoms. However, over time, clinical trials have shown treatments that focus on decreasing the underlying atherosclerosis processes—as opposed to simply treating symptoms—more effective.

In summary, the key to the more effective approaches has been better understanding of the widespread and insidious nature of the disease and to combine multiple different treatment strategies, not rely on just one or a few approaches. In addition, for those approaches, such as lipoprotein transport behaviors, which have been shown to produce the most success, adopting more aggressive combination treatment strategies has generally produced better results, both before and especially after people are symptomatic.

Because many blood thinners, particularly warfarin and salicylates such as aspirin, thin the blood by interfering with Vitamin K, there is recent evidence that blood thinners that work by this mechanism can actually worsen arterial calcification in the long term even though they thin the blood in the short term.^{[59] [60] [61] [62]}

Prognosis

Lipoprotein imbalances, upper normal and especially elevated blood sugar, i.e., diabetes and high blood pressure are risk factors for atherosclerosis; homocysteine, stopping smoking, taking anticoagulants (anti-clotting agents), which target clotting factors, taking omega-3 oils from fatty fish or plant oils such as flax or canola oils, exercising and losing weight are the usual focus of treatments that have proven to be helpful in clinical trials. The target serum cholesterol level is ideally equal or less than 4 mmol/L (160 mg/dL), and triglycerides equal or less than 2 mmol/L (180 mg/dL).

Evidence has increased that people with diabetes, despite not having clinically-detectable atherosclerotic disease, have more severe debility from atherosclerotic events over time than even non-diabetics that have already suffered atherosclerotic events. Thus diabetes has been upgraded to be viewed as an advanced atherosclerotic disease equivalent.

Research

An indication of the role of HDL on atherosclerosis has been with the rare Apo-A1 Milano human genetic variant of this HDL protein. A small short-term trial using bacterial synthesized human Apo-A1 Milano HDL in people with unstable angina produced fairly dramatic reduction in measured coronary plaque volume in only 6 weeks vs. the usual increase in plaque volume in those randomized to placebo. The trial was published in JAMA in early 2006. Ongoing work starting in the 1990s may lead to human clinical trials—probably by about 2008. These may use synthesized Apo-A1 Milano HDL directly. Or they may use gene-transfer methods to pass the ability to synthesize the Apo-A1 Milano HDLipoprotein.

Methods to increase high-density lipoprotein (HDL) particle concentrations, which in some animal studies largely reverses and remove atheromas, are being developed and researched.

Niacin has HDL raising effects (by 10 - 30%) and showed clinical trial benefit in the Coronary Drug Project and is commonly used in combination with other lipoprotein agents to improve efficacy of changing lipoprotein for the better. However most individuals have nuisance symptoms with short term flushing reactions, especially initially, and so working with a physician with a history of successful experience with niacin implementation, careful selection of brand, dosing strategy, etc. are usually critical to success.

However, increasing HDL by any means is not necessarily helpful. For example, the drug torcetrapib is the most effective agent currently known for raising HDL (by up to 60%). However, in clinical trials it also raised deaths by 60%. All studies regarding this drug were halted in December 2006.^[63]

The ERASE trial is a newer trial of an HDL booster, which has shown promise.^[64]

The ASTEROID trial used a high-dose of rosuvastatin—the statin with typically the most potent dose/response correlation track record (both for LDLipoproteins and HDLipoproteins.) It found plaque (intima + media volume) reduction.^[10] Several additional rosuvastatin treatment/placebo trials for evaluating other clinical outcomes are in progress.

The actions of macrophages drive atherosclerotic plaque progression. *Immunomodulation of atherosclerosis* is the term for techniques that modulate immune system function to suppress this macrophage action.^[65] Immunomodulation has been pursued with considerable success in both mice and rabbits since about 2002. Plans for human trials, hoped for by about 2008, are in progress.

Research on genetic expression and control mechanisms is progressing. Topics include

- PPAR, known to be important in blood sugar and variants of lipoprotein production and function;
- The multiple variants of the proteins that form the lipoprotein transport particles.

Some controversial research has suggested a link between atherosclerosis and the presence of several different nanobacteria in the arteries, e.g., *Chlamydophila pneumoniae*, though trials of current antibiotic treatments known to be usually effective in suppressing growth or killing these bacteria have not been successful in improving outcomes.^[66]

The immunomodulation approaches mentioned above, because they deal with innate responses of the host to promote atherosclerosis, have far greater prospects for success.

See also

- Angiogram
- Arterial stiffness
- Atheroma
- Chelation therapy
- Coronary circulation
- Coronary catheterization
- Fatty streaks
- Monckeberg's arteriosclerosis
- Intravascular ultrasound

Footnotes

- [1] <http://apps.who.int/classifications/apps/icd/icd10online/?gi70.htm+i70>
- [2] <http://www.icd9data.com/getICD9Code.ashx?icd9=440>
- [3] <http://www.icd9data.com/getICD9Code.ashx?icd9=414.0>
- [4] <http://www.diseasesdatabase.com/ddb1039.htm>
- [5] <http://www.nlm.nih.gov/medlineplus/ency/article/000171.htm>
- [6] <http://www.emedicine.com/med/topic182.htm>
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External links

- Atherosclerosis (http://www.dmoz.org/Health/Conditions_and_Diseases/Cardiovascular_Disorders/Vascular_Disorders/Atherosclerosis/) at the Open Directory Project
- A four-minute animation of the atherosclerosis process, entitled "Pathogenesis of Acute MI," commissioned by Paul M. Ridker, MD, MPH, FACC, FAHA, at the Harvard Medical School, can be viewed at pri-med.com (<http://www.pri-med.com/pmo/Home.aspx>).

Interventional cardiology

Interventional cardiology is a branch of the medical specialty of cardiology that deals specifically with the catheter based treatment of structural heart diseases. Andreas Gruentzig is considered the father of interventional cardiology.^[1]

A large number of procedures can be performed on the heart by catheterization. This most commonly involves the insertion of a sheath into the femoral artery (but, in practice, any large peripheral artery or vein) and cannulating the heart under X-ray visualization (most commonly fluoroscopy, a real-time x-ray. The radial artery may also be used for cannulation; this approach offers several advantages, including the accessibility of the artery in most patients, the easy control of bleeding even in anticoagulated patients, the enhancement of comfort because patients are capable of sitting up and walking immediately following the procedure, and the near absence of clinically significant sequelae in patients with a normal Allen test.^[2]

The main advantages of using the interventional cardiologic approach is the avoidance of the scars, pain, and long postoperative recovery associated with surgery. Additionally, the interventional cardiology procedure of primary angioplasty is now the gold standard of care for an acute myocardial infarction. It involves the extraction of clots from occluded coronary arteries, deployment of stents and balloons through a small hole made into a major artery, leaving no scars, which has given it the name "*pin-hole surgery*" (as opposed to "*key-hole surgery*").

Procedures performed by specialists in interventional cardiology:

Angioplasty

Also called percutaneous transluminal coronary angioplasty (PTCA), angioplasty is an intervention for the treatment of coronary artery disease.

Valvuloplasty

Valvuloplasty is the dilation of narrowed cardiac valves (usually mitral, aortic, or pulmonary).

Congenital heart defect correction

Percutaneous approaches can be employed to correct atrial septal and ventricular septal defects, closure of a patent ductus arteriosus, and angioplasty of the great vessels.

Percutaneous valve replacement: An alternative to open heart surgery, percutaneous valve replacement is the replacement of a heart valve using percutaneous methods.

Coronary thrombectomy

Coronary thrombectomy involves the removal of a thrombus (blood clot) from the coronary arteries.^[3]

Cardiac ablation

A technique performed by clinical electrophysiologists, cardiac ablation is used in the treatment of arrhythmias.

Surgery of the heart is done by the specialty of cardiothoracic surgery. Some interventional cardiology procedures are only performed when there is cardiothoracic surgery expertise in the hospital, in case of complications.

See also

- Interventional radiology
- Catheter
- Cannula
- Stent
- Restenosis

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External links

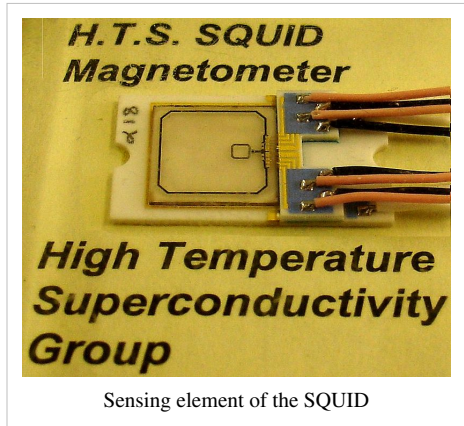
- tctmd.com (<http://www.tctmd.com/csportal/appmanager/tctmd/main>)
 - Angioplasty.Org (<http://www.angioplasty.org>)
 - European Association of Percutaneous Cardiovascular Interventions (EAPCI) (<http://www.escardio.org/COMMUNITIES/EAPCI/Pages/welcome.aspx>)
 - Interventional Portal: Relevant links for interventional cardiologists (<http://www.escardio.org/communities/EAPCI/portal/Pages/welcome.aspx>)
 - EuroPCROnline.com (<http://www.europcronline.com>)
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Non-invasive Cardiology Techniques and Methods

SQUID

A **SQUID** (for **superconducting quantum interference device**) is a very sensitive magnetometer used to measure extremely weak magnetic fields, based on superconducting loops containing Josephson junctions.

SQUIDs are sensitive enough to measure fields as low as 5 aT (5×10^{-18} T) within a few days of averaged measurements.^[1] Their noise levels are as low as $3 \text{ fT} \cdot \text{Hz}^{-1/2}$.^[2] For comparison, a typical refrigerator magnet produces 0.01 tesla (10^{-2} T), and some processes in animals produce very small magnetic fields between 10^{-9} T and 10^{-6} T. Recently invented SERF atomic magnetometers are potentially more sensitive and do not require cryogenic refrigeration but are orders of magnitude larger in size ($\sim 1 \text{ cm}^3$) and must be operated in a near-zero magnetic field.



History and design

There are two main types of SQUID: direct current (DC) and radio frequency (RF). RF SQUIDs can work with only one Josephson junction, which might make them cheaper to produce, but are less sensitive.

DC SQUID

The DC SQUID was invented in 1964 by Robert Jaklevic, John J. Lambe, James Mercereau, and Arnold Silver of Ford Research Labs after Brian David Josephson postulated the Josephson effect in 1962 and the first Josephson Junction was made by John Rowell and Philip Anderson at Bell Labs in 1963. It has two Josephson junctions in parallel in a superconducting loop. It is based on the DC Josephson effect. In the absence of any external magnetic field, the input current I splits into the two branches equally. Now, consider if a small amount of external flux is applied to the superconducting loop. This results in the screening currents that generate the magnetic field to cancel this applied external flux. The current in one of the branches of the superconducting loop is in the direction of I , and is equal to $I/2 + I_s/2$ and in the second branch is in the opposite direction of I and is equal to $I/2 - I_s/2$. As soon as the current in any one of the branches exceeds the critical current for the Josephson junction, the superconducting ring becomes resistive and a voltage appears across the junction. Now consider if the external flux is further increased and it now exceeds $\Phi_0/2$. Since the flux enclosed by the superconducting loop must be an integral number of the flux quanta, in this case the SQUID instead of screening the flux, energetically prefers to increase it to Φ_0 . The screening current now flows in the opposite direction. Thus the screening current changes direction every time the flux increases by half integer multiples of Φ_0 . Thus the critical current oscillates as a function of the applied flux. If the input current is more than I_c , then the SQUID always operates in the resistive mode. The voltage in this case is thus a function of the applied magnetic field and the period equal to Φ_0 . Since the current-voltage characteristics of the DC SQUID is hysteretic, a shunt resistance, R is connected across the junction to eliminate the hysteresis (although in the case of copper oxide based high temperature superconductors the junction's own intrinsic resistance is usually sufficient). The screening current is the applied flux divided by the self inductance of the ring. Thus $\Delta\Phi$ can be

estimated as the function of ΔV (flux to voltage converter).^{[3] [4] [5]} .

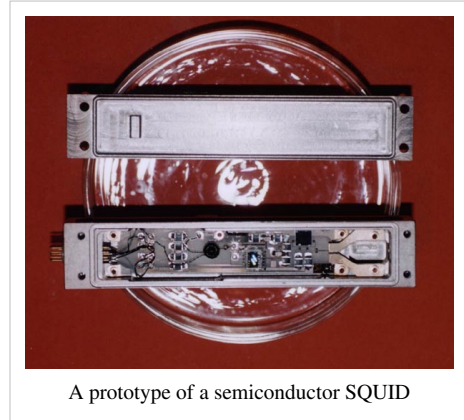
$$\Delta V = R \Delta I$$

$2I = 2 \Delta\Phi/L$, where L is the self inductance of the superconducting ring

$$\Delta V = (R/L) \Delta\Phi$$

RF SQUID

The RF SQUID was invented in 1965 by Robert Jaklevic, John J. Lambe, Arnold Silver, and James Edward Zimmerman at Ford.^[4] It is based on the AC Josephson effect and uses only one Josephson junction. It is less sensitive compared to DC SQUID but is cheaper and easier to manufacture in smaller quantities. The major part of fundamental measurements in biomagnetism even of extremely small signals have been performed, using RF SQUIDS (Tonotopic representation of the auditory cortex by Romani and Williamson 1980, brainstem auditory evoked magnetic field by Ern  et al. 1987^[6]). The RF SQUID is inductively coupled to a resonant tank circuit. Depending on the external magnetic field, as the SQUID operates in the resistive mode, the effective inductance of the tank circuit changes, thus changing the resonant frequency of the tank circuit. These frequency measurements can be easily done and thus the losses which appear as the voltage across the load resistor in the circuit are a periodic function of the applied magnetic flux with a period of Φ_0 . For a precise mathematical description refer to the original paper by Ern  et al.^[3] [7]



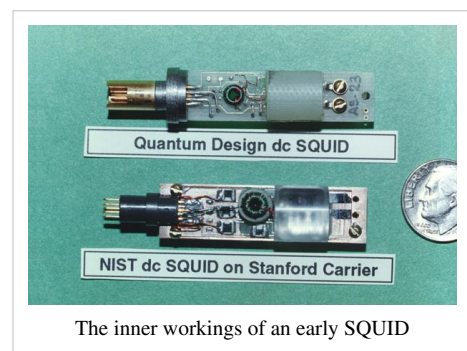
The traditional superconducting materials for SQUIDs are pure niobium or a lead alloy with 10% gold or indium, as pure lead is unstable when its temperature is repeatedly changed. To maintain superconductivity, the entire device needs to operate within a few degrees of absolute zero, cooled with liquid helium.

"High temperature" SQUID sensors are more recent; they are made of high temperature superconductors, particularly YBCO, and are cooled by liquid nitrogen which is cheaper and more easily handled than liquid helium. They are less sensitive than conventional "low temperature" SQUIDs but good enough for many applications.

Uses

The extreme sensitivity of SQUIDs makes them ideal for studies in biology. Magnetoencephalography (MEG), for example, uses measurements from an array of SQUIDs to make inferences about neural activity inside brains. Because SQUIDs can operate at acquisition rates much higher than the highest temporal frequency of interest in the signals emitted by the brain (kHz), MEG achieves good temporal resolution. Another area where SQUIDs are used is magnetogastrography, which is concerned with recording the weak magnetic fields of the stomach. A novel application of SQUIDs is the magnetic marker monitoring method, which is used to trace the path of orally applied drugs. In the clinical environment SQUIDs are used in cardiology for magnetic field imaging (MFI), which detects the magnetic field of the heart for diagnosis and risk stratification.

Probably the most common use of SQUIDs is in magnetic property measurement systems (MPMS). These are turn-key systems, made by several manufacturers, that measure the magnetic properties of a material sample. This is



typically done over a temperature range from that of 4 K to roughly 190 K, though higher temperatures mean less precision.

For example, SQUIDs are being used as detectors to perform magnetic resonance imaging (MRI). While high field MRI uses precession fields of one to several teslas, SQUID-detected MRI uses measurement fields that lie in the microtesla regime. Since the MRI signal drops off as the square of the magnetic field, a SQUID is used as the detector because of its extreme sensitivity. The SQUID coupled to a second-order gradiometer and input circuit, along with the application of gradients are the fundamental entities which allows a research group to retrieve noninvasive images. SQUID-detected MRI has advantages over high field MRI systems such as the low cost required to build such a system and its compactness. The principle has been proven by imaging human extremities, and its future application may involve tumor screening.

Another application is the scanning SQUID microscope, which uses a SQUID immersed in liquid helium as the probe. The use of SQUIDs in oil prospecting, mineral exploration, earthquake prediction and geothermal energy surveying is becoming more widespread as superconductor technology develops; they are also used as precision movement sensors in a variety of scientific applications, such as the detection of gravitational waves. Four SQUIDs were employed on Gravity Probe B in order to test the limits of the theory of general relativity.

It has also been suggested that they might be implemented in a quantum computer. These are the only macroscopic devices that have been cited as possible qubits in this context.

In fiction

- The science fiction writer William Gibson made reference to SQUIDs in his 1981 story "Johnny Mnemonic", where a genetically engineered ex-military dolphin uses a SQUID implant to read a memory device in the title character's brain.
- In the film *Strange Days*, SQUIDs are used to record and play back human memories, some of which are exchanged on the black market.
- In Michael Crichton's 1999 novel *Timeline*, SQUIDs are mentioned as a part of the quantum teleportation device developed by ITC.
- Jon Courtenay Grimwood's novel *redRobe* makes reference to SQUID probes being used to read memories and thoughts as part of a particularly invasive interrogation.
- SQUIDs are used as part of an advanced polygraph/fMRI machine in Neal Stephenson's novel *Snow Crash*.
- SQUIDS feature in the movie *Chemical Wedding*, where they are part of a supercomputer that is used to re-incarnate Aleister Crowley.
- In the movie *Watchmen* the explosive devices employed by Ozymandias display the text "S.Q.U.I.D. Initializing." This may be a reference to the scenario of an alien squid like creature in the original Comic Book which the bombs replaced.

See also

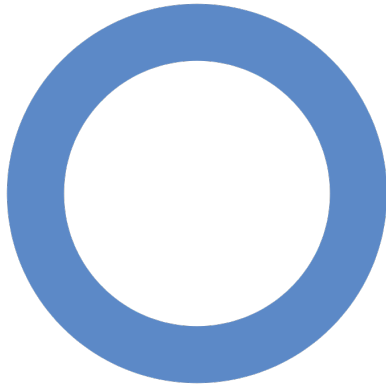
- Josephson Effect
 - Spallation Neutron Source
 - Mineral exploration
 - Geophysics
 - Electromagnetics
 - Vibrating sample magnetometer
-

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Diabetes type 2

Diabetes mellitus type 2

Diabetes mellitus type 2	
<i>Classification and external resources</i>	
	
Universal blue circle symbol for diabetes. ^[1]	
ICD-10	E 11. ^[2]
ICD-9	250.00, 250.02
DiseasesDB	3661 ^[3]
MedlinePlus	000313 ^[4]
eMedicine	article/117853 ^[5]
MeSH	D003924 ^[6]

Diabetes mellitus type 2 – formerly **non-insulin-dependent diabetes mellitus (NIDDM)** or **adult-onset diabetes** – is a metabolic disorder that is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency.^[7] Diabetes is often initially managed by increasing exercise and dietary modification. As the condition progresses, medications may be needed.

Unlike type 1 diabetes, there is very little tendency toward ketoacidosis though it is not unheard of.^[8] One effect that can occur is nonketonic hyperglycemia. Long-term complications from high blood sugar can include increased risk of heart attacks, strokes, amputation, and kidney failure.

Signs and symptoms

The classical symptoms of diabetes are polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased hunger), fatigue and weight loss.^[9]

Cause

Type 2 diabetes is due primarily to lifestyle factors and genetics.^[10] It was also found that oligomers of islet amyloid polypeptide (IAPP), a protein that forms amyloid deposits in the pancreas during type 2 diabetes, triggered the NLRP3 inflammasome and generated mature IL-1 β . One therapy for type 2 diabetes, glyburide, suppressed IAPP-mediated IL-1 β production in vitro.^[11]

Lifestyle

A number of lifestyle factors are known to be important to the development of type 2 diabetes. In one study, those who had high levels of physical activity, a healthy diet, did not smoke, and consumed alcohol in moderation had an 82% lower rate of diabetes. When a normal weight was included the rate was 89% lower. In this study a healthy diet was defined as one high in fiber, with a high polyunsaturated to saturated fat ratio, and a lower mean glycemic index.^[12] Obesity has been found to contribute to approximately 55% type 2 diabetes,^[13] and decreasing consumption of saturated fats and trans fatty acids while replacing them with unsaturated fats may decrease the risk.^[10] The increased rate of childhood obesity in between the 1960s and 2000s is believed to have led to the increase in type 2 diabetes in children and adolescents.^[14]

Environmental toxins may contribute to recent increases in the rate of type 2 diabetes. A positive correlation has been found between the concentration in the urine of bisphenol A, a constituent of some plastics, and the incidence of type 2 diabetes.^[15]

Medical conditions

There are many factors which can potentially give rise to or exacerbate type 2 diabetes. These include obesity, hypertension, elevated cholesterol (combined hyperlipidemia), and with the condition often termed metabolic syndrome (it is also known as Syndrome X, Reaven's syndrome, or CHAOS). Other causes include acromegaly, Cushing's syndrome, thyrotoxicosis, pheochromocytoma, chronic pancreatitis, cancer and drugs. Additional factors found to increase the risk of type 2 diabetes include aging,^[16] high-fat diets^[17] and a less active lifestyle.^[18]

Subclinical Cushing's syndrome (cortisol excess) may be associated with type 1 diabetes.^[19] The percentage of subclinical Cushing's syndrome in the diabetic population is about 9%.^[20] Diabetic patients with a pituitary microadenoma can improve insulin sensitivity by removal of these microadenomas.^[21]

Hypogonadism is often associated with cortisol excess, and testosterone deficiency is also associated with type 2 diabetes,^{[22] [23]} even if the exact mechanism by which testosterone improve insulin sensitivity is still not known.

Genetics

There is also a strong inheritable genetic connection in type 2 diabetes: having relatives (especially first degree) with type 2 increases risks of developing type 2 diabetes very substantially. In addition, there is also a mutation to the Islet Amyloid Polypeptide gene that results in an earlier onset, more severe, form of diabetes.^{[24] [25]}

About 55 percent of type 2 diabetes patients are obese at diagnosis^[26] —chronic obesity leads to increased insulin resistance that can develop into type 2 diabetes, most likely because adipose tissue (especially that in the abdomen around internal organs) is a (recently identified) source of several chemical signals to other tissues (hormones and cytokines).

Other research shows that type 2 diabetes causes obesity as an effect of the changes in metabolism and other deranged cell behavior attendant on insulin resistance.^[27]

However, environmental factors (almost certainly diet and weight) play a large part in the development of type 2 diabetes in addition to any genetic component. This can be seen from the adoption of the type 2 diabetes epidemiological pattern in those who have moved to a different environment as compared to the same genetic pool who have not. Immigrants to Western developed countries, for instance, as compared to lower incidence countries of origins.^[28]

There is a stronger inheritance pattern for type 2 diabetes. Those with first-degree relatives with type 2 diabetes have a much higher risk of developing type 2 diabetes, increasing with the number of those relatives. Concordance among monozygotic twins is close to 100%, and about 25% of those with the disease have a family history of diabetes. Genes significantly associated with developing type 2 diabetes, include *TCF7L2*, *PPARG*, *FTO*, *KCNJ11*, *NOTCH2*, *WFS1*, *CDKAL1*, *IGF2BP2*, *SLC30A8*, *JAZF1*, and *HHEX*.^[29] *KCNJ11* (potassium inwardly rectifying channel, subfamily J, member 11), encodes the islet ATP-sensitive potassium channel Kir6.2, and *TCF7L2* (transcription factor 7-like 2) regulates proglucagon gene expression and thus the production of glucagon-like peptide-1.^[30] Moreover, obesity (which is an independent risk factor for type 2 diabetes) is strongly inherited.^[31]

Monogenic forms, e.g., MODY, constitute 1–5 % of all cases.^[32]

Various hereditary conditions may feature diabetes, for example myotonic dystrophy and Friedreich's ataxia. Wolfram's syndrome is an autosomal recessive neurodegenerative disorder that first becomes evident in childhood. It consists of diabetes insipidus, diabetes mellitus, optic atrophy, and deafness, hence the acronym DIDMOAD.^[33]

Gene expression promoted by a diet of fat and glucose as well as high levels of inflammation related cytokines found in the obese results in cells that "produce fewer and smaller mitochondria than is normal," and are thus prone to insulin resistance.^[34]

Medications

Some drugs, used for any of several conditions, can interfere with the insulin regulation system, possibly producing drug induced hyperglycemia. Some examples follow, giving the biochemical mechanism in each case:

- Atypical Antipsychotics - Alter receptor binding characteristics, leading to increased insulin resistance.
 - Beta-blockers - Inhibit insulin secretion.
 - Calcium Channel Blockers - Inhibits secretion of insulin by interfering with cytosolic calcium release.
 - Corticosteroids - Cause peripheral insulin resistance and gluconeogenesis.
 - Fluoroquinolones - Inhibits insulin secretion by blocking ATP sensitive potassium channels.
 - Niacin - causes increased insulin resistance due to increased free fatty acid mobilization.
 - Phenothiazines - Inhibit insulin secretion.
 - Protease Inhibitors - Inhibit the conversion of proinsulin to insulin.
 - Somatropin - May decrease sensitivity to insulin, especially in those susceptible.
 - Thiazide Diuretics - Inhibit insulin secretion due to hypokalemia. They also cause increased insulin resistance due to increased free fatty acid mobilization.
-

Pathophysiology

Insulin resistance means that body cells do not respond appropriately when insulin is present. Unlike type 1 diabetes mellitus, insulin resistance is generally "post-receptor", meaning it is a problem with the cells that respond to insulin rather than a problem with the production of insulin.

This is a more complex problem than type 1, but is sometimes easier to treat, especially in the early years when insulin is often still being produced internally. Severe complications can result from improperly managed type 2 diabetes, including renal failure, erectile dysfunction, blindness, slow healing wounds (including surgical incisions), and arterial disease, including coronary artery disease. The onset of type 2 diabetes has been most common in middle age and later life, although it is being more frequently seen in adolescents and young adults due to an increase in child obesity and inactivity. A type of diabetes called MODY is increasingly seen in adolescents, but this is classified as a diabetes due to a specific cause and not as type 2 diabetes.

Diabetes mellitus with a known etiology, such as secondary to other diseases, known gene defects, trauma or surgery, or the effects of drugs, is more appropriately called secondary diabetes mellitus or diabetes due to a specific cause. Examples include diabetes mellitus such as MODY or those caused by hemochromatosis, pancreatic insufficiencies, or certain types of medications (e.g., long-term steroid use).

Diagnosis

2006 WHO Diabetes diagnosis criteria^[35]

Condition	2 hour glucose	Fasting glucose
	mmol/l(mg/dl)	mmol/l(mg/dl)
Normal	<7.8 (<140)	<6.1 (<110)
Diabetes mellitus	≥11.1 (≥200)	≥7.0 (≥126)

The World Health Organization definition of diabetes is for a single raised glucose reading with symptoms, otherwise raised values on two occasions, of either:^[36]

- fasting plasma glucose ≥ 7.0 mmol/l (126 mg/dl)
- or
- With a glucose tolerance test, two hours after the oral dose a plasma glucose ≥ 11.1 mmol/l (200 mg/dl)

Accuracy of tests for early detection

If a 2-hour postload glucose level of at least 11.1 mmol/L (≥ 200 mg/dL) is used as the reference standard, the fasting plasma glucose > 7.0 mmol/L (126 mg/dL) diagnoses *current* diabetes with^[37]:

- sensitivity about 50%
- specificity greater than 95%

A *random* capillary blood glucose > 6.7 mmol/L (120 mg/dL) diagnoses *current* diabetes with^[38]:

- sensitivity = 75%
- specificity = 88%

Glycosylated hemoglobin values that are elevated (over 5%), but not in the diabetic range (not over 7.0%) are predictive of *subsequent* clinical diabetes in United States female health professionals.^[39] In this study, 177 of 1061 patients with glycosylated hemoglobin value less than 6% became diabetic within 5 years compared to 282 of 26281 patients with a glycosylated hemoglobin value of 6.0% or more. This equates to a glycosylated hemoglobin value of 6.0% or more having:

- sensitivity = 16.7%
- specificity = 98.9%

Benefit of early detection

Since publication of the USPSTF statement, a randomized controlled trial of prescribing acarbose to patients with "high-risk population of men and women between the ages of 40 and 70 years with a body mass index (BMI), calculated as weight in kilograms divided by the square of height in meters, between 25 and 40. They were eligible for the study if they had IGT according to the World Health Organization criteria, plus impaired fasting glucose (a fasting plasma glucose concentration of between 100 and 140 mg/dL or 5.5 and 7.8 mmol/L) found a number needed to treat of 44 (over 3.3 years) to prevent a major cardiovascular event.^[40]

Other studies have shown that lifestyle changes,^[41] orlistat^[42] and metformin^[43] can delay the onset of diabetes.

Screening

Diabetes screening is recommended for many people at various stages of life, and for those with any of several risk factors. The screening test varies according to circumstances and local policy, and may be a random blood glucose test, a fasting blood glucose test, a blood glucose test two hours after 75 g of glucose, or an even more formal glucose tolerance test. Many healthcare providers recommend universal screening for adults at age 40 or 50, and often periodically thereafter. Earlier screening is typically recommended for those with risk factors such as obesity, family history of diabetes, history of gestational diabetes, high-risk ethnicity (Hispanic, Native American, Afro-Caribbean, Pacific Islander, or Māori).^[44] ^[45]

Many medical conditions are associated with diabetes and warrant screening. A partial list includes: subclinical Cushing's syndrome,^[19] testosterone deficiency,^[22] high blood pressure, past gestational diabetes, polycystic ovary syndrome, chronic pancreatitis, fatty liver, cystic fibrosis, several mitochondrial neuropathies and myopathies (such as MIDD), myotonic dystrophy, Friedreich's ataxia, some of the inherited forms of neonatal hyperinsulinism. The risk of diabetes is higher with chronic use of several medications, including long term corticosteroids, some chemotherapy agents (especially L-asparaginase), as well as some of the antipsychotics and mood stabilizers (especially phenothiazines and some atypical antipsychotics).

People with a confirmed diagnosis of diabetes are tested routinely for complications. This includes yearly urine testing for microalbuminuria and examination of the retina of the eye for retinopathy.

Prevention

Onset of type 2 diabetes can often be delayed through proper nutrition and regular exercise.^[46]

Interest has arisen in preventing diabetes due to research on the benefits of treating patients before overt diabetes. Although the U.S. Preventive Services Task Force concluded that "the evidence is insufficient to recommend for or against routinely screening asymptomatic adults for type 2 diabetes, impaired glucose tolerance, or impaired fasting glucose,"^[37] ^[47] this was a grade I recommendation^[48] when published in 2003. However, the USPSTF does recommend screening for diabetics in adults with hypertension or hyperlipidemia.^[49]

In 2005, an evidence report^[50] by the Agency for Healthcare Research and Quality concluded that "there is evidence that combined diet and exercise, as well as drug therapy (metformin, acarbose), may be effective at preventing progression to diabetes in IGT subjects".^[51]

Milk has also been associated with the prevention of diabetes. A questionnaire study was done by Choi et al. of 41,254 men which including a twelve year follow up showed this association. In this study, it was found that diets high in low-fat dairy might lower the risk of type 2 diabetes in men. Even though these benefits are being considered linked to milk consumption, the effect of diet is only one factor that is affecting the body's overall health.^[52]

Lifestyle

Type 2 diabetes risk can be reduced in many cases by making changes in diet and increasing physical activity.^{[41] [53]}^[54] The American Diabetes Association (ADA) recommends maintaining a healthy weight, getting at least 2½ hours of exercise per week (several brisk sustained walks appear sufficient), having a modest fat intake, and eating sufficient fiber (e.g., from whole grains).

There is inadequate evidence that eating foods of low glycemic index is clinically helpful despite recommendations and suggested diets emphasizing this approach.^[55]

Diets that are very low in saturated fats reduce the risk of becoming insulin resistant and diabetic.^{[56] [57]} Study group participants whose "physical activity level and dietary, smoking, and alcohol habits were all in the low-risk group had an 82% lower incidence of diabetes."^[12] In another study of dietary practice and incidence of diabetes, "foods rich in vegetable oils, including non-hydrogenated margarines, nuts, and seeds, should replace foods rich in saturated fats from meats and fat-rich dairy products. Consumption of partially hydrogenated fats should be minimized."^[10]

There are numerous studies which suggest connections between some aspects of type 2 diabetes with ingestion of certain foods or with some drugs. Breastfeeding may also be associated with the prevention of type 2 diabetes in mothers.^[58]

Medications

Some studies have shown delayed progression to diabetes in predisposed patients through prophylactic use of metformin,^[53] rosiglitazone,^[59] or valsartan.^[60] In patients on hydroxychloroquine for rheumatoid arthritis, incidence of diabetes was reduced by 77% though causal mechanisms are unclear.^[61] Lifestyle interventions are however more effective than metformin at preventing diabetes regardless of weightloss.^[62]

Management

Left untreated, type 2 diabetes is a chronic, progressive condition, but there are well-established treatments which can delay or prevent entirely the formerly inevitable consequences of the condition. Often, the condition is viewed as progressive since poor management of blood sugar leads to a myriad of steadily worsening complications. However, if blood sugar is properly maintained, then the condition is, in a limited sense, cured - that is, patients are at no heightened risk for neuropathy, blindness, or any other high blood sugar complication, though the underlying issue, a tendency to hyperglycemia has not been addressed directly. A study at UCLA in 2005 showed that the Pritikin Program of diet and exercise brought dramatic improvement to a group of diabetics and pre-diabetics in only three weeks, so that about half no longer met the criteria for the condition.^{[63] [64] [65]}

There are two main goals of treatment:

1. reduction of mortality and concomitant morbidity (from assorted diabetic complications)
2. preservation of quality of life

The first goal can be achieved through close glycemic control (i.e., to near 'normal' blood glucose levels); the reduction in severity of diabetic side effects has been very well demonstrated in several large clinical trials and is established beyond controversy. The second goal is often addressed (in developed countries) by support and care from teams of diabetic health workers (usually physician, PA, nurse, dietitian or a certified diabetic educator). Endocrinologists, family practitioners, and general internists are the physician specialties most likely to treat people with diabetes. Knowledgeable patient participation is vital to clinical success, and so patient education is a crucial aspect of this effort.

Type 2 diabetes is initially treated by adjustments in diet and exercise, and by weight loss, most especially in obese patients. The amount of weight loss which improves the clinical picture is sometimes modest (2–5 kg or 4.4-11 lb); this is almost certainly due to currently poorly understood aspects of fat tissue activity, for instance chemical

signaling (especially in visceral fat tissue in and around abdominal organs). In many cases, such initial efforts can substantially restore insulin sensitivity. In some cases strict diet can adequately control the glycemic levels.

Diabetes education is an integral component of medical care.

Goals

Treatment goals for type 2 diabetic patients are related to effective control of blood glucose, blood pressure and lipids to minimize the risk of long-term consequences associated with diabetes. They are suggested in clinical practice guidelines released by various national and international diabetes agencies.

The targets are:

- Hb_{A1c} of 6%^[66] to 7.0%^[67]
- Preprandial blood glucose: 4.0 to 6.0 mmol/L (72 to 108 mg/dl)^[68]
- 2-hour postprandial blood glucose: 5.0 to 8.0 mmol/L (90 to 144 mg/dl)^[68]

In older patients, clinical practice guidelines by the American Geriatrics Society states "for frail older adults, persons with life expectancy of less than 5 years, and others in whom the risks of intensive glycemic control appear to outweigh the benefits, a less stringent target such as Hb_{A1c} of 8% is appropriate".^[69]

Lifestyle modification

Exercise

In September 2007, a joint randomized controlled trial by the University of Calgary and the University of Ottawa found that "Either aerobic or resistance training alone improves glycemic control in type 2 diabetes, but the improvements are greatest with combined aerobic and resistance training than either alone."^[70] ^[71] The combined program reduced the HbA1c by 0.5 percentage point. Other studies have established that the amount of exercise needed is not large or extreme, but must be consistent and continuing. Examples might include a brisk 45 minute walk every other day.

Theoretically, exercise does have benefits in that exercise would stimulate the release of certain ligands that cause GLUT4 to be released from internal endosomes to the cell membrane. Insulin though, which no longer works effectively in those afflicted with type 2 diabetes, causes GLUT1 to be placed into the membrane. Exercise also allows for the uptake of glucose independently of insulin, i.e. by adrenaline.

Dietary management

Modifying the diet to limit and control glucose (or glucose equivalent, e.g., starch) intake, and in consequence, blood glucose levels, is known to assist type 2 patients, especially early in the course of the condition's progression. Additionally, weight loss is recommended and is often helpful in persons suffering from type 2 diabetes (see above).

Monitoring of blood glucose

Self-monitoring of blood glucose may not improve outcomes in some cases, especially those of "reasonably well controlled non-insulin treated patients with type 2 diabetes".^[72] Nevertheless, it is very strongly recommended for patients in whom it can assist in maintaining proper glycemic control^[73], and is well worth the cost (sometimes considerable) if it does. It is the only source of current information on the glycemic state of the body, as changes are rapid and frequent, depending on food, exercise, and medication (dosage and timing with respect to both diet and exercise), and secondarily, on time of day, stress (mental and physical), infection, etc. However, patient adherence to self-monitoring routines is often sporadic and prone to fluctuation, with patients often self-monitoring very regularly near to check-up times and very little during other times.^[73] Ensuring due compliance is an ongoing issue which may well affect research results into efficacy and benefits of self-monitoring.

The National Institute for Health and Clinical Excellence (NICE), UK released updated diabetes recommendations on 30 May 2008. They indicate that self-monitoring of blood glucose levels for people with newly diagnosed type 2

diabetes should be part of a structured self-management education plan.^[74] However, a recent study found that a treatment strategy of intensively lowering blood sugar levels (below 6%) in patients with additional cardiovascular disease risk factors poses more harm than benefit, and so there appear to be limits to benefit of intensive blood glucose control in some patients.^{[75] [76]}

Medications

There are several drugs available for type 2 diabetics—most are unsuitable or even dangerous for use by type 1 diabetics. They fall into several classes and are not equivalent, nor can they be simply substituted one for another. All are prescription drugs.

One of the most widely used drugs now used for type 2 diabetes is the biguanide metformin; it works primarily by reducing liver release of blood glucose from glycogen stores and secondarily by provoking some increase in cellular uptake of glucose in body tissues. Metformin also reduces insulin resistance and is preferred in obese patients as it promotes weight loss. Both historically and currently the most commonly used drugs are in the Sulfonylurea group, of which several members (including glibenclamide and gliclazide) are widely used; these increase glucose stimulated insulin secretion by the pancreas and so lower blood glucose even in the face of insulin resistance. Their chief adverse effect is increased chance of hypoglycemic episodes.



Metformin 500mg tablets

Newer drug classes include:

- Thiazolidinediones (TZDs) (rosiglitazone, pioglitazone, and troglitazone -- the last, as Rezulin, was withdrawn from the US market because of an increased risk of systemic acidosis). These increase tissue insulin sensitivity by affecting gene expression
- α -glucosidase inhibitors (acarbose and miglitol) which interfere with absorption of some glucose containing nutrients, reducing (or at least slowing) the amount of glucose absorbed
- Meglitinides which stimulate insulin release (nateglinide, repaglinide, and their analogs) quickly; they can be taken with food, unlike the sulfonylureas which must be taken prior to food (sometimes some hours before, depending on the drug)
- Peptide analogs which work in a variety of ways:
 - Incretin mimetics which increase insulin output from the beta cells among other effects. These includes the Glucagon-like peptide (GLP) analog exenatide, sometimes referred to as *lizard spit* as it was first identified in Gila monster saliva
 - Dipeptidyl peptidase-4 (DPP-4) inhibitors increase Incretin levels (sitagliptin) by decreasing their deactivation rates
 - Amylin agonist analog, which slows gastric emptying and suppresses glucagon (pramlintide)

Oral

A systematic review of randomized controlled trials found that metformin and second-generation sulfonylureas are the preferred choices for most with type 2 diabetes, especially those early in the course of the condition.^[77] Failure of response after a time is not unknown with most of these agents: the initial choice of anti-diabetic drug has been compared in a randomized controlled trial which found "cumulative incidence of monotherapy failure at 5 years to be 15% with rosiglitazone, 21% with metformin, and 34% with glyburide".^[78] Of these, rosiglitazone users showed more weight gain and edema than did non-users.^[78] Rosiglitazone may increase risk of death from cardiovascular causes though the causal connection is unclear.^[79] Pioglitazone and rosiglitazone may also increase the risk of

fractures.^{[80] [80]}

For patients who also have heart failure, metformin may be the best tolerated drug.^[81]

The variety of available agents can be confusing, and the clinical differences among type 2 diabetes patients compounds the problem. At present, choice of drugs for type 2 diabetics is rarely straightforward and in most instances has elements of repeated trial and adjustment.

Injectable peptide analogs

DPP-4 inhibitors (also known as glyptins) lowered HbA1c by 0.74% (points), comparable to other antidiabetic drugs.^[82] GLP-1 analogs resulted in weight loss and had more gastrointestinal side effects, while DPP-4 inhibitors were generally weight neutral and increased risk for infection and headache, but both classes appear to present an alternative to other antidiabetic drugs. However, weight gain and/or hypoglycaemia have been observed when DPP-4 inhibitors were used with sulfonylureas; effect on long-term health and morbidity rates are still unknown.^[83]

Insulin

In rare cases, if antidiabetic drugs fail (i.e., the clinical benefit stops), insulin therapy may be necessary – usually in addition to oral medication therapy – to maintain normal or near normal glucose levels.^{[84] [85]}

Typical total daily dosage of insulin is 0.6 U/kg.^[86] But, of course, best timing and indeed total amounts depend on diet (composition, amount, and timing) as well the degree of insulin resistance. More complicated estimations to guide initial dosage of insulin are:^[87]

- For men, [(fasting plasma glucose [mmol/liter]–5)×2] × (weight [kg]÷(14.3×height [m])–height [m])
- For women, [(fasting plasma glucose [mmol/liter]–5)×2] × (weight [kg]÷(13.2×height [m])–height [m])

The initial insulin regimen are often chosen based on the patient's blood glucose profile.^[88] Initially, adding nightly insulin to patients failing oral medications may be best.^[89] Nightly insulin combines better with metformin than with sulfonylureas.^[86] The initial dose of nightly insulin (measured in IU/d) should be equal to the fasting blood glucose level (measured in mmol/L). If the fasting glucose is reported in mg/dl, multiply by 0.05551 to convert to mmol/L.^[90]

When nightly insulin is insufficient, choices include:

- Premixed insulin with a fixed ratio of short and intermediate acting insulin; this tends to be more effective than long acting insulin, but is associated with increased hypoglycemia.^{[91] [92] [93]} Initial total daily dosage of biphasic insulin can be 10 units if the fasting plasma glucose values are less than 180 mg/dl or 12 units when the fasting plasma glucose is above 180 mg/dl.^[92] A guide to titrating fixed ratio insulin is available.^[88]
- Long acting insulins such as insulin glargine and insulin detemir. A meta-analysis of randomized controlled trials by the Cochrane Collaboration found "only a minor clinical benefit of treatment with long-acting insulin analogues for patients with diabetes mellitus type 2".^[94] More recently, a randomized controlled trial found that although long acting insulins were less effective, they were associated with reduced hypoglycemic episodes.^[91]
- Insulin Pump therapy in type 2 diabetes is gradually becoming popular. In an original published study, in addition to reduction of blood sugars, there is evidence of profound benefits in resistant neuropathic pain and also improvements in sexual performance.^[95]

Gastric bypass surgery

Gastric Bypass procedures are currently considered an elective procedure with no universally accepted algorithm to decide who should have the surgery. In the diabetic patient, certain types result in 99-100% prevention of insulin resistance and 80-90% clinical resolution or remission of type 2 diabetes. In 1991, the NIH (National Institutes of Health) Consensus Development Conference on Gastrointestinal Surgery for Obesity proposed that the body mass index (BMI) threshold to consider surgery should drop from 40 to 35 in the appropriate patient. More recently, the American Society for Bariatric Surgery (ASBS) and the ASBS Foundation suggested that the BMI threshold be

lowered to 30 in the presence of severe co-morbidities.^[96] Debate has flourished about the role of gastric bypass surgery in type 2 diabetics since the publication of The Swedish Obese Subjects Study. The largest prospective series showed a large decrease in the occurrence of type 2 diabetes in the post-gastric bypass patient at both 2 years (odds ratio was 0.14) and at 10 years (odds ratio was 0.25).^[97]

A study of 20-years of Greenville (US) gastric bypass patients found that 80% of those with type 2 diabetes before surgery no longer required insulin or oral agents to maintain normal glucose levels. Weight loss occurred rapidly in many people in the study who had had the surgery. The 20% who did not respond to bypass surgery were, typically, those who were older and had had diabetes for over 20 years.^[98]

In January 2008, the Journal of the American Medical Association (JAMA) published the first randomized controlled trial comparing the efficacy of laparoscopic adjustable gastric banding against conventional medical therapy in the obese patient with type 2 diabetes. Laparoscopic Adjustable Gastric Banding results in remission of type 2 diabetes among affected patients diagnosed within the previous two years according to a randomized controlled trial.^[99] The relative risk reduction was 69.0%. For patients at similar risk to those in this study (87.0% had type 2), this leads to an absolute risk reduction of 60%. 1.7 patients must be treated for one to benefit (number needed to treat = 1.7). Click here^[100] to adjust these results for patients at higher or lower risk of type 2 diabetes.

These results have not yet produced a clinical standard for surgical treatment of type 2 diabetes, as the mechanism, if any, is currently obscure. Surgical cure of type 2 diabetes must be, as a result, considered currently experimental.

Epidemiology

There are an estimated 23.6 million people in the United States (7.8% of the population) with diabetes with 17.9 million being diagnosed,^[101] 90% of whom are type 2.^[102] With prevalence rates doubling between 1990 and 2005, CDC has characterized the increase as an epidemic.^[103] Traditionally considered a disease of adults, type 2 diabetes is increasingly diagnosed in children in parallel to rising obesity rates^[104] due to alterations in dietary patterns as well as in life styles during childhood.^[105]

About 90–95% of all North American cases of diabetes are type 2,^[106] and about 20% of the population over the age of 65 has type 2 diabetes. The incidence of type 2 diabetes in other parts of the world varies substantially, almost certainly because of environmental and lifestyle factors, though these are not known in detail. Diabetes affects over 150 million people worldwide and this number is expected to double by 2025.^[106]

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External links

- Diabetes mellitus type 2 (http://www.dmoz.org/Health/Conditions_and_Diseases/Endocrine_Disorders/Pancreas/Diabetes/Type_2/) at the Open Directory Project
- Diabetes mellitus type 2 (http://www.healthplus24.com/Diseases_and_Conditions1/Diabetes.aspx)
- Type 2 Diabetes - General Information (<http://www.diabetes.co.uk/type2-diabetes.html>)

Organizations

- IDF Diabetes Atlas (<http://www.diabetesatlas.org/>)
- International Diabetes Federation (<http://www.idf.org/>)
- World Diabetes Day (International Diabetes Federation) (<http://www.worlddiabetesday.org/>)
- Diabetes UK - Largest organisation in the UK working for people with diabetes (<http://www.diabetes.org.uk/>)
- American Diabetes Association (<http://www.diabetes.org/home.jsp>)

Authorities

- National Diabetes Information Clearinghouse (<http://diabetes.niddk.nih.gov/>)
- Centers for Disease Control (Endocrine pathology) (<http://www.cdc.gov/diabetes/>)

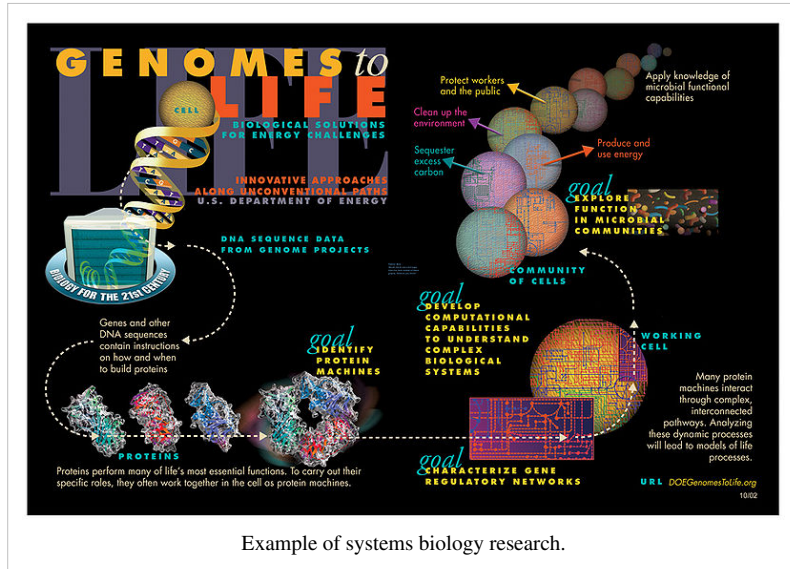
Further reading

- Diabetes Symptoms Revisited: Are They Too Vague and Too Late? (<http://www.seasonalmagazine.com/2009/07/diabetes-symptoms-revisited-are-they.html>)
 - ABC Radio National transcript on hypothesised aetiology involving gut hormone (<http://www.abc.net.au/rn/scienceshow/stories/2009/2554683.htm>)
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Complex Systems Biology, Genetic Screening and Biostatistics

Complex Systems Biology

Systems biology is a term used to describe a number of trends in bioscience research, and a movement which draws on those trends. Proponents describe systems biology as a biology-based inter-disciplinary study field that focuses on complex interactions in biological systems, claiming that it uses a new perspective (holism instead of reduction). Particularly from year 2000 onwards, the term is used widely in the biosciences, and in a variety of contexts. An often stated ambition of systems biology is the modeling and discovery of emergent properties, properties of a system whose theoretical description is only possible using techniques which fall under the remit of systems biology.



Overview

Systems biology can be considered from a number of different aspects:

- As a **field of study**, particularly, the study of the interactions between the components of *biological systems*, and how these interactions give rise to the function and behavior of that system (for example, the enzymes and metabolites in a metabolic pathway).^{[1] [2]}
- As a **paradigm**, usually defined in antithesis to the so-called reductionist paradigm (biological organisation), although fully consistent with the scientific method. The distinction between the two paradigms is referred to in these quotations:

"The reductionist approach has successfully identified most of the components and many of the interactions but, unfortunately, offers no convincing concepts or methods to understand how system properties emerge...the pluralism of causes and effects in biological networks is better addressed by observing, through quantitative measures, multiple components simultaneously and by rigorous data integration with mathematical models" Science^[3]

"Systems biology...is about putting together rather than taking apart, integration rather than reduction. It requires that we develop ways of thinking about integration that are as rigorous as our reductionist programmes, but different....It means changing our philosophy, in the full sense of the term" Denis Noble^[4]

- As a series of **operational protocols used for performing research**, namely a cycle composed of theory, analytic or computational modelling to propose specific testable hypotheses about a biological system,

experimental validation, and then using the newly acquired quantitative description of cells or cell processes to refine the computational model or theory.^{[5] [6]} Since the objective is a model of the interactions in a system, the experimental techniques that most suit systems biology are those that are system-wide and attempt to be as complete as possible. Therefore, transcriptomics, metabolomics, proteomics and high-throughput techniques are used to collect quantitative data for the construction and validation of models.

- As the application of dynamical systems theory to molecular biology.
- As a **socioscientific phenomenon** defined by the strategy of pursuing integration of complex data about the interactions in biological systems from diverse experimental sources using interdisciplinary tools and personnel.

This variety of viewpoints is illustrative of the fact that systems biology refers to a cluster of peripherally overlapping concepts rather than a single well-delineated field. However the term has widespread currency and popularity as of 2007, with chairs and institutes of systems biology proliferating worldwide.

History

Systems biology finds its roots in:

- the quantitative modeling of enzyme kinetics, a discipline that flourished between 1900 and 1970,
- the mathematical modeling of population growth,
- the simulations developed to study neurophysiology, and
- control theory and cybernetics.

One of the theorists who can be seen as one of the precursors of systems biology is Ludwig von Bertalanffy with his general systems theory^[7]. One of the first numerical simulations in biology was published in 1952 by the British neurophysiologists and Nobel prize winners Alan Lloyd Hodgkin and Andrew Fielding Huxley, who constructed a mathematical model that explained the action potential propagating along the axon of a neuronal cell.^[8] Their model described a cellular function emerging from the interaction between two different molecular components, a potassium and a sodium channels, and can therefore be seen as the beginning of computational systems biology.^[9] In 1960, Denis Noble developed the first computer model of the heart pacemaker.^[10]

The formal study of systems biology, as a distinct discipline, was launched by systems theorist Mihajlo Mesarovic in 1966 with an international symposium at the Case Institute of Technology in Cleveland, Ohio entitled "Systems Theory and Biology."^{[11] [12]}

The 1960s and 1970s saw the development of several approaches to study complex molecular systems, such as the Metabolic Control Analysis and the biochemical systems theory. The successes of molecular biology throughout the 1980s, coupled with a skepticism toward theoretical biology, that then promised more than it achieved, caused the quantitative modelling of biological processes to become a somewhat minor field.

However the birth of functional genomics in the 1990s meant that large quantities of high quality data became available, while the computing power exploded, making more realistic models possible. In 1997, the group of Masaru Tomita published the first quantitative model of the metabolism of a whole (hypothetical) cell.

Around the year 2000, after Institutes of Systems Biology were established in Seattle and Tokyo, systems biology emerged as a movement in its own right, spurred on by the completion of various genome projects, the large increase in data from the omics (e.g. genomics and proteomics) and the accompanying advances in high-throughput experiments and bioinformatics. Since then, various research institutes dedicated to systems biology have been developed. As of summer 2006, due to a shortage of people in systems biology^[13] several doctoral training centres in systems biology have been established in many parts of the world.

Disciplines associated with systems biology

According to the interpretation of Systems Biology as the ability to obtain, integrate and analyze complex data from multiple experimental sources using interdisciplinary tools, some typical technology platforms are:

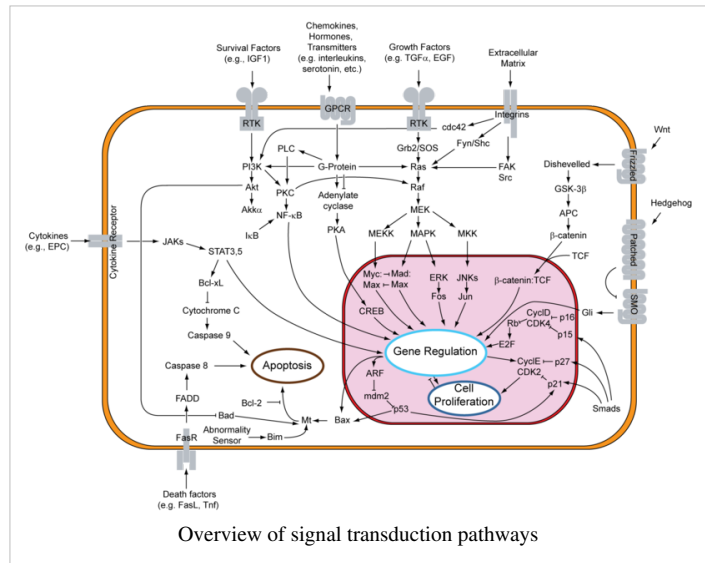
- **Phenomics:** Organismal variation in phenotype as it changes during its life span..
- **Genomics:** Organismal deoxyribonucleic acid (DNA) sequence, including intra-organisamal cell specific variation. (i.e. Telomere length variation etc.).
- **Epigenomics / Epigenetics:** Organismal and corresponding cell specific transcriptomic regulating factors not empirically coded in the genomic sequence. (i.e. DNA methylation, Histone Acetelation etc.).
- **Transcriptomics:** Organismal, tissue or whole cell gene expression measurements by DNA microarrays or serial analysis of gene expression
- **Interferomics:** Organismal, tissue, or cell level transcript correcting factors (i.e. RNA interference)
- **Translatomics / Proteomics:** Organismal, tissue, or cell level measurements of proteins and peptides via two-dimensional gel electrophoresis, mass spectrometry or multi-dimensional protein identification techniques (advanced HPLC systems coupled with mass spectrometry). Sub disciplines include phosphoproteomics, glycoproteomics and other methods to detect chemically modified proteins.
- **Metabolomics:** Organismal, tissue, or cell level measurements of all small-molecules known as metabolites.
- **Glycomics:** Organismal, tissue, or cell level measurements of carbohydrates.
- **Lipidomics:** Organismal, tissue, or cell level measurements of lipids.

In addition to the identification and quantification of the above given molecules further techniques analyze the dynamics and interactions within a cell. This includes:

- **Interactomics:** Organismal, tissue, or cell level study of interactions between molecules. Currently the authoratative molecular discipline in this field of study is protein-protein interactions (PPI), although the working definition does not pre-clude inclusion of other molecular disciplines such as those defined here.
- **Fluxomics:** Organismal, tissue, or cell level measurements of molecular dynamic changes over time.
- **Biomics:** systems analysis of the biome.

The investigations are frequently combined with large scale perturbation methods, including gene-based (RNAi, mis-expression of wild type and mutant genes) and chemical approaches using small molecule libraries. Robots and automated sensors enable such large-scale experimentation and data acquisition. These technologies are still emerging and many face problems that the larger the quantity of data produced, the lower the quality. A wide variety of quantitative scientists (computational biologists, statisticians, mathematicians, computer scientists, engineers, and physicists) are working to improve the quality of these approaches and to create, refine, and retest the models to accurately reflect observations.

The systems biology approach often involves the development of mechanistic models, such as the reconstruction of dynamic systems from the quantitative properties of their elementary building blocks.^{[14] [15]} For instance, a cellular network can be modelled mathematically using methods coming from chemical kinetics and control theory. Due to the large number of parameters, variables and constraints in cellular networks, numerical and computational techniques are often used. Other aspects of computer science and informatics are also used in systems biology. These



include new forms of computational model, such as the use of process calculi to model biological processes, the integration of information from the literature, using techniques of information extraction and text mining, the development of online databases and repositories for sharing data and models, approaches to database integration and software interoperability via loose coupling of software, websites and databases, or commercial suits, and the development of syntactically and semantically sound ways of representing biological models.

See also

Related fields

- Bioinformatics
- Biological network inference
- Biological systems engineering
- Biomedical cybernetics
- Biostatistics
- Computational biology
- Computational systems biology
- Complex systems
- Complex systems biology
- Extrapolation based molecular systems biology
- Theoretical Biophysics
- Network Biology
- Relational Biology
- Translational Research
- Scotobiology
- Synthetic biology
- Systems biology modeling
- Systems ecology
- Systems genetics
- Systems immunology

Related terms

- Life
- Biological organisation
- Artificial life
- Gene regulatory network
- Metabolic network modelling
- Living systems theory
- Network Theory of Aging
- Regulome
- Systems Biology Markup Language (SBML)
- Systems Biology Graphical Notation (SBGN)
- SBO
- Viable System Model
- Antireductionism

Systems biologists

- Category:Systems biologists

Lists

- Category:Systems biologists
- List of systems biology conferences
- List of omics topics in biology
- List of publications in systems biology
- List of systems biology research groups
- List of systems biology visualization software

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External links

- Institute for Systems Biology: SBI (<http://www.systemsbiology.org>)
- Applied BioDynamics Laboratory: Boston University (<http://www.bu.edu/abl/>)
- Institute for Research in Immunology and Cancer (IRIC): Université de Montréal (<http://www.irc.ca>)
- Systems Biology - BioChemWeb.org (<http://www.biochemweb.org/systems.shtml>)
- Systems Biology Portal (<http://www.systems-biology.org/>) - administered by the Systems Biology Institute
- Semantic Systems Biology (<http://www.semantic-systems-biology.org>)
- SystemsX.ch (<http://www.systemsx.ch/>) - The Swiss Initiative in Systems Biology
- Systems Biology at the Pacific Northwest National Laboratory (<http://www.sysbio.org/>)
- Institute of Bioinformatics and Systems Biology (<http://bioinfo.nctu.edu.tw/>), National Chiao Tung University, Taiwan

In Weaver's view, disorganized complexity results from the particular system having a very large number of parts, say millions of parts, or many more. Though the interactions of the parts in a "disorganized complexity" situation can be seen as largely random, the properties of the system as a whole can be understood by using probability and statistical methods.

A prime example of disorganized complexity is a gas in a container, with the gas molecules as the parts. Some would suggest that a system of disorganized complexity may be compared, for example, with the (relative) simplicity of the planetary orbits—the latter can be known by applying Newton's laws of motion, though this example involved highly correlated events.

Organized complexity, in Weaver's view, resides in nothing else than the non-random, or correlated, interaction between the parts. These correlated relationships create a differentiated structure which can, as a system, interact with other systems. The coordinated system manifests properties not carried by, or dictated by, individual parts. The organized aspect of this form of complexity vis a vis other systems than the subject system can be said to "emerge," without any "guiding hand".

HOW TO READ MAP:

The above map is a conceptual and historical overview of complexity science.

The Map is to be read as follows:

First, the Map is roughly historical, working as a timeline that is divided into five major periods that one can read from left to right: 1) old-school, 2) percolation, 3) the new science of complexity, 4) a work in progress, and 5) recent developments.

Each fields of study is represented as double-lined ellipse, with a double-lined arrow moving from left to the right. The relative size of these ellipses is meaningless, and is strictly a function of the space needed to write the name of each field. Double-lined arrows represent the trajectory of each field of study. Space constraints required that the length of these arrows be limited; readers should therefore assume that all of them extend outward to 2006.

The decision where to place the various fields of research relative to one another is somewhat arbitrary. However, we did try to position relative to some degree of intellectual similarity. For example, those sciences oriented toward the study of systems are located at the top of the map; the sciences that tend to extend outward from or around cybernetics and artificial intelligence and are oriented toward the development of computational method are located at the bottom.

Areas of research identified for each field of study are represented as single-lined circles. As with the fields of study, the size of these circles is strictly a function of the space needed to write the different names.

The intellectual links amongst the fields of study and amongst the areas of research are represented with a bold, single-lined arrow. The head of the arrow indicates the direction of the relationship. In some cases, the relationship is mutual. To keep the map simple, rather than draw this link to the trajectory for a field of study or area of research (as in the case of the reciprocal relationship between complexity science and agent-based modeling), we draw it to the ellipse representing the field of study or area of research.

For each area of research, we also include a short list of the leading scholars. This list is not exhaustive; but it is representative, based on number of citations, general recognition, and importance in the historical development of the area of research. For each scholar we provide the following information: name, most widely known contribution, and links to key areas of research. The links amongst the scholars and their respective areas of research are represented by a dashed line. One will also note that the names of the scholars differ in font size. This was done to demonstrate their relative importance within complexity science and the sociology of complexity.

Because of the diversity of research in complexity science, we focused on the key topics in the field.

Map legend

The number of parts does not have to be very large for a particular system to have emergent properties. A system of organized complexity may be understood in its properties (behavior among the properties) through modeling and simulation, particularly modeling and simulation with computers. An example of organized complexity is a city neighborhood as a living mechanism, with the neighborhood people among the system's parts.^[4]

Sources and factors of complexity

The source of disorganized complexity is the large number of parts in the system of interest, and the lack of correlation between elements in the system.

There is no consensus at present on general rules regarding the sources of organized complexity, though the lack of randomness implies correlations between elements. See e.g. Robert Ulanowicz's treatment of ecosystems.^[5] Consistent with prior statements here, the number of parts (and types of parts) in the system and the number of relations between the parts would have to be non-trivial—however, there is no general rule to separate "trivial" from "non-trivial".

Complexity of an object or system is a relative property. For instance, for many functions (problems), such a computational complexity as time of computation is smaller when multitape Turing machines are used than when Turing machines with one tape are used. Random Access Machines allow one to even more decrease time complexity (Greenlaw and Hoover 1998: 226), while inductive Turing machines can decrease even the complexity class of a function, language or set (Burgin 2005). This shows that tools of activity can be an important factor of complexity.

Specific meanings of complexity

In several scientific fields, "complexity" has a specific meaning :

- In computational complexity theory, the amounts of resources required for the execution of algorithms is studied. The most popular types of computational complexity are the time complexity of a problem equal to the number of steps that it takes to solve an instance of the problem as a function of the size of the input (usually measured in bits), using the most efficient algorithm, and the space complexity of a problem equal to the volume of the memory used by the algorithm (e.g., cells of the tape) that it takes to solve an instance of the problem as a function of the size of the input (usually measured in bits), using the most efficient algorithm. This allows to classify computational problems by complexity class (such as P, NP ...). An axiomatic approach to computational complexity was developed by Manuel Blum. It allows one to deduce many properties of concrete computational complexity measures, such as time complexity or space complexity, from properties of axiomatically defined measures.
- In algorithmic information theory, the *Kolmogorov complexity* (also called *descriptive complexity*, *algorithmic complexity* or *algorithmic entropy*) of a string is the length of the shortest binary program which outputs that string. Different kinds of Kolmogorov complexity are studied: the uniform complexity, prefix complexity, monotone complexity, time-bounded Kolmogorov complexity, and space-bounded Kolmogorov complexity. An axiomatic approach to Kolmogorov complexity based on Blum axioms (Blum 1967) was introduced by Mark Burgin in the paper presented for publication by Andrey Kolmogorov (Burgin 1982). The axiomatic approach encompasses other approaches to Kolmogorov complexity. It is possible to treat different kinds of Kolmogorov complexity as particular cases of axiomatically defined generalized Kolmogorov complexity. Instead, of proving similar theorems, such as the basic invariance theorem, for each particular measure, it is possible to easily deduce all such results from one corresponding theorem proved in the axiomatic setting. This is a general advantage of the axiomatic approach in mathematics. The axiomatic approach to Kolmogorov complexity was further developed in the book (Burgin 2005) and applied to software metrics (Burgin and Debnath, 2003; Debnath and Burgin, 2003).
- In information processing, complexity is a measure of the total number of properties transmitted by an object and detected by an observer. Such a collection of properties is often referred to as a state.
- In business, complexity describes the variances and their consequences in various fields such as product portfolio, technologies, markets and market segments, locations, manufacturing network, customer portfolio, IT systems, organization, processes etc.
- In physical systems, complexity is a measure of the probability of the state vector of the system. This should not be confused with entropy; it is a distinct mathematical measure, one in which two distinct states are never conflated and considered equal, as is done for the notion of entropy statistical mechanics.
- In mathematics, Krohn-Rhodes complexity is an important topic in the study of finite semigroups and automata.
- In software engineering, programming complexity is a measure of the interactions of the various elements of the software. This differs from the computational complexity described above in that it is a measure of the design of the software.

There are different specific forms of complexity:

- In the sense of how complicated a problem is from the perspective of the person trying to solve it, limits of complexity are measured using a term from cognitive psychology, namely the *hairy limit*.
- Complex adaptive system denotes systems which have some or all of the following attributes^[6]
 - The number of parts (and types of parts) in the system and the number of relations between the parts is non-trivial – however, there is no general rule to separate "trivial" from "non-trivial";
 - The system has memory or includes feedback;
 - The system can adapt itself according to its history or feedback;

- The relations between the system and its environment are non-trivial or non-linear;
- The system can be influenced by, or can adapt itself to, its environment; and
- The system is highly sensitive to initial conditions.

Study of complexity

Complexity has always been a part of our environment, and therefore many scientific fields have dealt with complex systems and phenomena. Indeed, some would say that only what is somehow complex—what displays variation without being random—is worthy of interest.

The use of the term complex is often confused with the term complicated. In today's systems, this is the difference between myriad connecting "stovepipes" and effective "integrated" solutions.^[7] This means that complex is the opposite of independent, while complicated is the opposite of simple.

While this has led some fields to come up with specific definitions of complexity, there is a more recent movement to regroup observations from different fields to study complexity in itself, whether it appears in anthills, human brains, or stock markets. One such interdisciplinary group of fields is relational order theories.

Complexity topics

Complex behaviour

The behaviour of a complex system is often said to be due to emergence and self-organization. Chaos theory has investigated the sensitivity of systems to variations in initial conditions as one cause of complex behaviour.

Complex mechanisms

Recent developments around artificial life, evolutionary computation and genetic algorithms have led to an increasing emphasis on complexity and complex adaptive systems.

Complex simulations

In social science, the study on the emergence of macro-properties from the micro-properties, also known as macro-micro view in sociology. The topic is commonly recognized as social complexity that is often related to the use of computer simulation in social science, i.e.: computational sociology.

Complex systems

Systems theory has long been concerned with the study of complex systems (In recent times, *complexity theory* and *complex systems* have also been used as names of the field). These systems can be biological, economic, technological, etc. Recently, complexity is a natural domain of interest of the real world socio-cognitive systems and emerging systemics research. Complex systems tend to be high-dimensional, non-linear and hard to model. In specific circumstances they may exhibit low dimensional behaviour.

Complexity in data

In information theory, algorithmic information theory is concerned with the complexity of strings of data.

Complex strings are harder to compress. While intuition tells us that this may depend on the codec used to compress a string (a codec could be theoretically created in any arbitrary language, including one in which the very small command "X" could cause the computer to output a very complicated string like "18995316"), any two Turing-complete languages can be implemented in each other, meaning that the length of two encodings in different languages will vary by at most the length of the "translation" language—which will end up being negligible for sufficiently large data strings.

These algorithmic measures of complexity tend to assign high values to random noise. However, those studying complex systems would not consider randomness as complexity.

Information entropy is also sometimes used in information theory as indicative of complexity.

Applications of complexity

Computational complexity theory is the study of the complexity of problems—that is, the difficulty of solving them. Problems can be classified by complexity class according to the time it takes for an algorithm—usually a computer program—to solve them as a function of the problem size. Some problems are difficult to solve, while others are easy. For example, some difficult problems need algorithms that take an exponential amount of time in terms of the size of the problem to solve. Take the travelling salesman problem, for example. It can be solved in time $O(n^2 2^n)$ (where n is the size of the network to visit—let's say the number of cities the travelling salesman must visit exactly once). As the size of the network of cities grows, the time needed to find the route grows (more than) exponentially. Even though a problem may be computationally solvable in principle, in actual practice it may not be that simple. These problems might require large amounts of time or an inordinate amount of space. Computational complexity may be approached from many different aspects. Computational complexity can be investigated on the basis of time, memory or other resources used to solve the problem. Time and space are two of the most important and popular considerations when problems of complexity are analyzed.

There exist a certain class of problems that although they are solvable in principle they require so much time or space that it is not practical to attempt to solve them. These problems are called intractable.

There is another form of complexity called hierarchical complexity. It is orthogonal to the forms of complexity discussed so far, which are called horizontal complexity

See also

- Chaos theory
 - Command and Control Research Program
 - Complexity theory (disambiguation page)
 - Cyclomatic complexity
 - Digital morphogenesis
 - Evolution of complexity
 - Game complexity
 - Holism in science
 - Interconnectedness
 - Model of Hierarchical Complexity
 - Names of large numbers
 - Network science
 - Network theory
 - Novelty theory
 - Occam's razor
 - Process architecture
 - Programming Complexity
 - Sociology and complexity science
 - Systems theory
 - Variety (cybernetics)
 - Volatility, uncertainty, complexity and ambiguity
-

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External links

- Quantifying Complexity Theory (<http://www.calresco.org/lucas/quantify.htm>) – classification of complex systems
- Complexity Measures (<http://cscs.umich.edu/~crshalizi/notebooks/complexity-measures.html>) – an article about the abundance of not-that-useful complexity measures.
- UC Four Campus Complexity Videoconferences (<http://eclectic.ss.uci.edu/~drwhite/center/cac.html>) – Human Sciences and Complexity
- Complexity Digest (<http://comdig.unam.mx/>) – networking the complexity community
- The Santa Fe Institute (<http://www.santafe.edu/>) – engages in research in complexity related topics
- Exploring Complexity in Science and Technology (<http://web.cecs.pdx.edu/~mm/ExploringComplexityFall2009/index.html>) – A introductory course about complex system by Melanie Mitchell

Complex adaptive system

Complex adaptive systems are special cases of complex systems. They are *complex* in that they are dynamic networks of interactions and relationships not aggregations of static entities. They are adaptive in that their individual and collective behaviour changes as a result of experience.^[1]

Overview

The term *complex adaptive systems*, or *complexity science*, is often used to describe the loosely organized academic field that has grown up around the study of such systems. Complexity science is not a single theory—it encompasses more than one theoretical framework and is highly interdisciplinary, seeking the answers to some fundamental questions about living, adaptable, changeable systems.

Examples of complex adaptive systems include the stock market, social insect and ant colonies, the biosphere and the ecosystem, the brain and the immune system, the cell and the developing embryo, manufacturing businesses and any human social group-based endeavour in a cultural and social system such as political parties or communities. There are close relationships between the field of CAS and artificial life. In both areas the principles of emergence and self-organization are very important.

The ideas and models of CAS are essentially evolutionary, grounded in modern chemistry, biological views on adaptation, exaptation and evolution and simulation models in economics and social systems.

Definitions

A CAS is a complex, self-similar collection of interacting adaptive agents. The study of CAS focuses on complex, emergent and macroscopic properties of the system. Various definitions have been offered by different researchers:

- John H. Holland

A Complex Adaptive System (CAS) is a dynamic network of many agents (which may represent cells, species, individuals, firms, nations) acting in parallel, constantly acting and reacting to what the other agents are doing. The control of a CAS tends to be highly dispersed and decentralized. If there is to be any coherent behavior in the system, it has to arise from competition and cooperation among the agents themselves. The overall behavior of the system is the result of a huge number of decisions made every moment by many individual

agents.^[2]

A CAS behaves/evolves according to three key principles: order is emergent as opposed to predetermined (c.f. Neural Networks), the system's history is irreversible, and the system's future is often unpredictable. The basic building blocks of the CAS are agents. Agents scan their environment and develop schema representing interpretive and action rules. These schema are subject to change and evolution.^[3]

- Other definitions

Macroscopic collections of simple (and typically nonlinear) interacting units that are endowed with the ability to evolve and adapt to a changing environment.^[4]

General properties

What distinguishes a CAS from a pure multi-agent system (MAS) is the focus on top-level properties and features like self-similarity, complexity, emergence and self-organization. A MAS is simply defined as a system composed of multiple interacting agents. In CASs, the agents as well as the system are adaptive: the system is self-similar. A CAS is a complex, self-similar collectivity of interacting adaptive agents. Complex Adaptive Systems are characterised by a high degree of adaptive capacity, giving them resilience in the face of perturbation.

Other important properties are adaptation (or homeostasis), communication, cooperation, specialization, spatial and temporal organization, and of course reproduction. They can be found on all levels: cells specialize, adapt and reproduce themselves just like larger organisms do. Communication and cooperation take place on all levels, from the agent to the system level. The forces driving co-operation between agents in such a system can, in some cases be analysed with game theory.

Characteristics

Complex adaptive systems are characterised as follows^[5] and the most important are:

- The number of elements is sufficiently large that a conventional description (e.g. a system of differential equations) are not only impractical, but cease to assist in understanding the system, the elements also have to interact and the interaction must be dynamic. Interactions can be physical or involve the exchange of information.
- Such interactions are rich, i.e. any element in the system is affected and affects several other systems.
- The interactions are non-linear which means that small causes can have large results.
- Interactions are primarily but not exclusively with immediate neighbours and the nature of the influence is modulated.
- Any interaction can feed back onto itself directly or after a number of intervening stages, such feedback can vary in quality. This is known as *recurrency*.
- Such systems are open and it may be difficult or impossible to define system boundaries
- Complex systems operate under far from equilibrium conditions, there has to be a constant flow of energy to maintain the organisation of the system
- All complex systems have a history, they evolve and their past is co-responsible for their present behaviour
- Elements in the system are ignorant of the behaviour of the system as a whole responding only to what is available to it locally

Axelrod & Cohen^[6] identify a series of key terms from a modeling perspective:

- **Strategy**, a conditional action pattern that indicates what to do in which circumstances
- **Artifact**, a material resource that has definite location and can respond to the action of agents
- **Agent**, a collection of properties, strategies & capabilities for interacting with artifacts & other agents
- **Population**, a collection of agents, or, in some situations, collections of strategies
- **System**, a larger collection, including one or more populations of agents and possibly also artifacts.
- **Type**, all the agents (or strategies) in a population that have some characteristic in common

- **Variety**, the diversity of types within a population or system
- **Interaction pattern**, the recurring regularities of contact among types within a system
- **Space (physical)**, location in geographical space & time of agents and artifacts
- **Space (conceptual)**, “location” in a set of categories structured so that “nearby” agents will tend to interact
- **Selection**, processes that lead to an increase or decrease in the frequency of various types of agent or strategies
- **Success criteria** or **performance measures**, a “score” used by an agent or designer in attributing credit in the selection of relatively successful (or unsuccessful) strategies or agents.

Evolution of complexity

Living organisms are complex adaptive systems. Although complexity is hard to quantify in biology, evolution has produced some remarkably complex organisms.^[7] This observation has led to the common misconception of evolution being progressive and leading towards what are viewed as “higher organisms”.^[8]

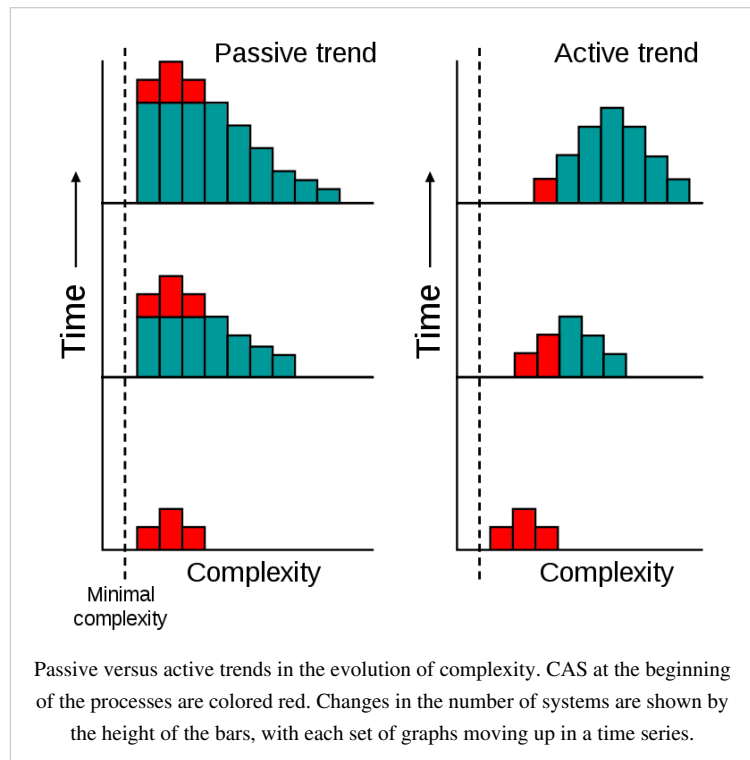
If this were generally true, evolution would possess an active trend towards complexity. As shown below, in this type of process the value of the most common amount of complexity would increase over time.^[9] Indeed, some artificial life simulations have suggested that the generation of CAS is an inescapable feature of evolution.^{[10] [11]}

However, the idea of a general trend towards complexity in evolution can also be explained through a passive process.^[9] This

involves an increase in variance but the most common value, the mode, does not change. Thus, the maximum level of complexity increases over time, but only as an indirect product of there being more organisms in total. This type of random process is also called a bounded random walk.

In this hypothesis, the apparent trend towards more complex organisms is an illusion resulting from concentrating on the small number of large, very complex organisms that inhabit the right-hand tail of the complexity distribution and ignoring simpler and much more common organisms. This passive model emphasizes that the overwhelming majority of species are microscopic prokaryotes,^[12] which comprise about half the world's biomass^[13] and constitute the vast majority of Earth's biodiversity.^[14] Therefore, simple life remains dominant on Earth, and complex life appears more diverse only because of sampling bias.

This lack of an overall trend towards complexity in biology does not preclude the existence of forces driving systems towards complexity in a subset of cases. These minor trends are balanced by other evolutionary pressures that drive systems towards less complex states.



See also

- Agent-based model
- Artificial life
- Center for Complex Systems and Brain Sciences
- Center for Social Dynamics & Complexity (CSDC) at Arizona State University^[15]
- Cognitive Science
- Command and Control Research Program
- Complex system
- Computational Sociology
- Enterprise systems engineering
- Generative sciences
- Santa Fe Institute
- Simulated reality
- Sociology and complexity science
- Swarm Development Group

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External links

- Complexity Digest (<http://www.comdig.org/>) comprehensive digest of latest CAS related news and research.
- DNA Wales Research Group (<http://www.dnawales.co.uk/>) Current Research in Organisational change CAS/CES related news and free research data. Also linked to the Business Doctor & BBC documentary series
- A description (<http://pespmc1.vub.ac.be/CAS.html>) of complex adaptive systems on the Principia Cybernetica Web.
- Quick reference (<http://bactra.org/notebooks/complexity.html>) single-page description of the 'world' of complexity and related ideas hosted by the Center for the Study of Complex Systems at the University of Michigan.
- Complex systems research network (<http://www.complexsystems.net.au/>)
- The Open Agent-Based Modeling Consortium (<http://www.openabm.org/site/>)

Computational biology

Computational biology is an interdisciplinary field that applies the techniques of computer science, applied mathematics and statistics to address biological problems. The main focus lies in the development of computational and statistical data analysis methods and in developing mathematical modeling and computational simulation techniques. By these means it addresses scientific research topics with their theoretical and experimental questions without a laboratory. It is connected to the following fields:

- Computational biomodeling, a field concerned with building computer models of biological systems.
 - Bioinformatics, which applies algorithms and statistical techniques to the interpretation, classification and understanding of biological datasets. These typically consist of large numbers of DNA, RNA, or protein sequences. Sequence alignment is used to assemble the datasets for analysis. Comparisons of homologous sequences, gene finding, and prediction of gene expression are the most common techniques used on assembled datasets; however, analysis of such datasets have many applications throughout all fields of biology.
 - Mathematical biology aims at the mathematical representation, treatment and modeling of biological processes, using a variety of applied mathematical techniques and tools.
 - Computational genomics, a field within genomics which studies the genomes of cells and organisms. High-throughput genome sequencing produces lots of data, which requires extensive post-processing (genome assembly) and uses DNA microarray technologies to perform statistical analyses on the genes expressed in individual cell types. This can help find genes of interest for certain diseases or conditions. This field also studies the mathematical foundations of sequencing.
 - Molecular modeling, which consists of modelling the behaviour of molecules of biological importance.
 - Protein structure prediction and structural genomics, which attempt to systematically produce accurate structural models for three-dimensional protein structures that have not been determined experimentally.
 - Computational biochemistry and biophysics, which make extensive use of structural modeling and simulation methods such as molecular dynamics and Monte Carlo method-inspired Boltzmann sampling methods in an
-

attempt to elucidate the kinetics and thermodynamics of protein functions.

Biostatistics

Biostatistics (a contraction of biology and statistics; sometimes referred to as **biometry** or **biometrics**) is the application of statistics to a wide range of topics in biology. The science of biostatistics encompasses the design of biological experiments, especially in medicine and agriculture; the collection, summarization, and analysis of data from those experiments; and the interpretation of, and inference from, the results.

Biostatistics and the history of biological thought

Biostatistical reasoning and modeling were of critical importance to the foundation theories of modern biology. In the early 1900s, after the rediscovery of Mendel's work, the conceptual gaps in understanding between genetics and evolutionary Darwinism led to vigorous debate between biometricians such as Walter Weldon and Karl Pearson and Mendelians such as Charles Davenport, William Bateson and Wilhelm Johannsen. By the 1930s statisticians and models built on statistical reasoning had helped to resolve these differences and to produce the neo-Darwinian modern evolutionary synthesis.

The leading figures in the establishment of this synthesis all relied on statistics and developed its use in biology.

- Sir Ronald A. Fisher developed several basic statistical methods in support of his work *The Genetical Theory of Natural Selection*
- Sewall G. Wright used statistics in the development of modern population genetics
- J. B. S Haldane's book, *The Causes of Evolution*, reestablished natural selection as the premier mechanism of evolution by explaining it in terms of the mathematical consequences of Mendelian genetics.

These individuals and the work of other biostatisticians, mathematical biologists, and statistically inclined geneticists helped bring together evolutionary biology and genetics into a consistent, coherent whole that could begin to be quantitatively modeled.

In parallel to this overall development, the pioneering work of D'Arcy Thompson in *On Growth and Form* also helped to add quantitative discipline to biological study.

Despite the fundamental importance and frequent necessity of statistical reasoning, there may nonetheless have been a tendency among biologists to distrust or deprecate results which are not qualitatively apparent. One anecdote describes Thomas Hunt Morgan banning the Friden calculator from his department at Caltech, saying "Well, I am like a guy who is prospecting for gold along the banks of the Sacramento River in 1849. With a little intelligence, I can reach down and pick up big nuggets of gold. And as long as I can do that, I'm not going to let any people in my department waste scarce resources in placer mining."^[1] Educators are now adjusting their curricula to focus on more quantitative concepts and tools.^[2]

Education and training programs

Almost all educational programmes in biostatistics are at postgraduate level. They are most often found in schools of public health, affiliated with schools of medicine, forestry, or agriculture or as a focus of application in departments of statistics.

In the United States, while several universities have dedicated biostatistics departments, many other top-tier universities integrate biostatistics faculty into statistics or other departments, such as epidemiology. Thus departments carrying the name "biostatistics" may exist under quite different structures. For instance, relatively new biostatistics departments have been founded with a focus on bioinformatics and computational biology, whereas older departments, typically affiliated with schools of public health, will have more traditional lines of research

involving epidemiological studies and clinical trials as well as bioinformatics. In larger universities where both a statistics and a biostatistics department exist, the degree of integration between the two departments may range from the bare minimum to very close collaboration. In general, the difference between a statistics program and a biostatistics one is twofold: (i) statistics departments will often host theoretical/methodological research which are less common in biostatistics programs and (ii) statistics departments have lines of research that may include biomedical applications but also other areas such as industry (quality control), business and economics and biological areas other than medicine.

Applications of biostatistics

- Public health, including epidemiology, health services research, nutrition, and environmental health
- Design and analysis of clinical trials in medicine
- Population genetics, and statistical genetics in order to link variation in genotype with a variation in phenotype. This has been used in agriculture to improve crops and farm animals (animal breeding). In biomedical research, this work can assist in finding candidates for gene alleles that can cause or influence predisposition to disease in human genetics
- Analysis of genomics data, for example from microarray or proteomics experiments ^[3] ^[4]. Often concerning diseases or disease stages ^[5].
- Ecology, ecological forecasting
- Biological sequence analysis ^[6]
- Systems biology for gene network inference or pathways analysis

Statistical methods are beginning to be integrated into medical informatics, public health informatics, bioinformatics and computational biology.

Biostatistics journals

- *Biometrics*
 - *Biometrika*
 - *Biostatistics*
 - *International Journal of Biostatistics, The*
 - *Canadian Journal of Epidemiology and Biostatistics* ^[7]
 - *Journal of Agricultural, Biological, and Environmental Statistics*
 - *Journal of Biopharmaceutical Statistics*
 - *Pharmaceutical Statistics*
 - *Statistical Applications in Genetics and Molecular Biology*
 - *Statistics in Biopharmaceutical Research*
 - *Statistics in Medicine*
 - *Turkiye Klinikleri Journal of Biostatistics*
-

Related fields

Biostatistics shares several methods with quantitative fields such as:

- computational biology
- computer science,
- operations research,
- psychometrics,
- statistics,
- econometrics, and
- mathematical demography

See also

- Ecological forecasting
- Group size measures
- Machine Learning
- Network Biology
- Quantitative parasitology
- Systems Biology

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- [3] Helen Causton, John Quackenbush and Alvis Brazma (2003). "Statistical Analysis of Gene Expression Microarray Data". Wiley-Blackwell.
- [4] Terry Speed (2003). "Microarray Gene Expression Data Analysis: A Beginner's Guide". Chapman & Hall/CRC.
- [5] Frank Emmert-Streib and Matthias Dehmer (2010). "Medical Biostatistics for Complex Diseases". Wiley-Blackwell.
- [6] Warren J. Ewens and Gregory R. Grant (2004). "Statistical Methods in Bioinformatics: An Introduction". Springer.
- [7] <http://www.cjeb.ca/>

External links

- The International Biometric Society (<http://www.tibs.org>)
- The Collection of Biostatistics Research Archive (<http://www.biostatsresearch.com/repository/>)
- Guide to Biostatistics (MedPageToday.com) (<http://www.medpagetoday.com/Medpage-Guide-to-Biostatistics.pdf>)
- Biostatistician (<http://biostatistician.eu>)

Journals

- Statistical Applications in Genetics and Molecular Biology (<http://www.bepress.com/sagmb/>)
- Statistics in Medicine (<http://www3.interscience.wiley.com/cgi-bin/jhome/2988>)
- The International Journal of Biostatistics (<http://www.bepress.com/ijb/>)
- Journal of Agricultural, Biological, and Environmental Statistics (<http://www.amstat.org/publications/jabes/>)
- Journal of Biopharmaceutical Statistics (<http://www.tandf.co.uk/journals/titles/10543406.asp>)
- Biostatistics (<http://www.biostatistics.oxfordjournals.org/>)
- Biometrics (<http://www.tibs.org/biometrics/>)
- Biometrika (<http://biomet.oxfordjournals.org/>)
- Biometrical Journal (<http://www.biometrical-journal.de/>)
- Genetics Selection Evolution (<http://www.gse-journal.org/>)

Bioinformatics

Bioinformatics is the application of statistics and computer science to the field of molecular biology.

The term *bioinformatics* was coined by Paulien Hogeweg in 1979 for the study of informatic processes in biotic systems. Its primary use since at least the late 1980s has been in genomics and genetics, particularly in those areas of genomics involving large-scale DNA sequencing.

Bioinformatics now entails the creation and advancement of databases, algorithms, computational and statistical techniques and theory to solve formal and practical problems arising from the management and analysis of biological data.

Over the past few decades rapid developments in genomic and other molecular research technologies and developments in information technologies have combined to produce a tremendous amount of information related to molecular biology. It is the name given to these mathematical and computing approaches used to glean understanding of biological processes.

Common activities in bioinformatics include mapping and analyzing DNA and protein sequences, aligning different DNA and protein sequences to compare them and creating and viewing 3-D models of protein structures.

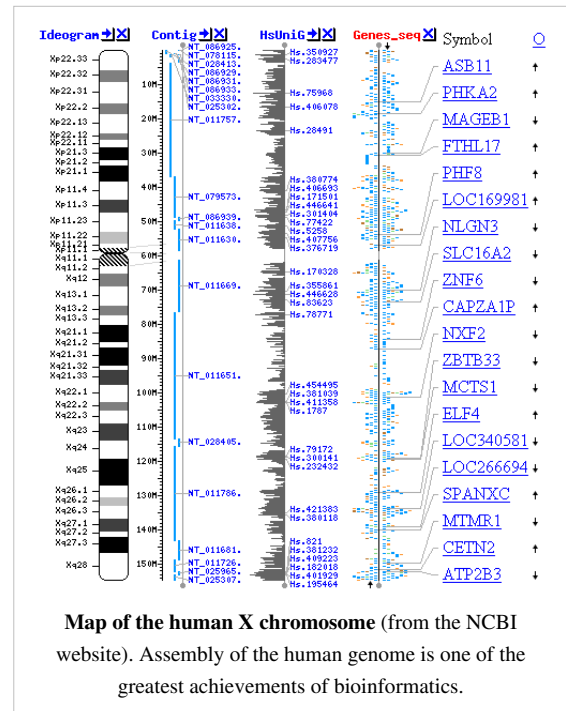
The primary goal of bioinformatics is to increase the understanding of biological processes. What sets it apart from other approaches, however, is its focus on developing and applying computationally intensive techniques (e.g., pattern recognition, data mining, machine learning algorithms, and visualization) to achieve this goal. Major research efforts in the field include sequence alignment, gene finding, genome assembly, drug design, drug discovery, protein structure alignment, protein structure prediction, prediction of gene expression and protein-protein interactions, genome-wide association studies and the modeling of evolution.

Introduction

Bioinformatics was applied in the creation and maintenance of a database to store biological information at the beginning of the "genomic revolution", such as nucleotide and amino acid sequences. Development of this type of database involved not only design issues but the development of complex interfaces whereby researchers could both access existing data as well as submit new or revised data.

In order to study how normal cellular activities are altered in different disease states, the biological data must be combined to form a comprehensive picture of these activities. Therefore, the field of bioinformatics has evolved such that the most pressing task now involves the analysis and interpretation of various types of data, including nucleotide and amino acid sequences, protein domains, and protein structures. The actual process of analyzing and interpreting data is referred to as computational biology. Important sub-disciplines within bioinformatics and computational biology include:

- the development and implementation of tools that enable efficient access to, and use and management of, various types of information.
- the development of new algorithms (mathematical formulas) and statistics with which to assess relationships among members of large data sets, such as methods to locate a gene within a sequence, predict protein structure



and/or function, and cluster protein sequences into families of related sequences.

Major research areas

Sequence analysis

Since the Phage Φ -X174 was sequenced in 1977, the DNA sequences of thousands of organisms have been decoded and stored in databases. This sequence information is analyzed to determine genes that encode polypeptides (proteins), RNA genes, regulatory sequences, structural motifs, and repetitive sequences. A comparison of genes within a species or between different species can show similarities between protein functions, or relations between species (the use of molecular systematics to construct phylogenetic trees). With the growing amount of data, it long ago became impractical to analyze DNA sequences manually. Today, computer programs such as BLAST are used daily to search the genomes of thousands of organisms, containing billions of nucleotides. These programs can compensate for mutations (exchanged, deleted or inserted bases) in the DNA sequence, in order to identify sequences that are related, but not identical. A variant of this sequence alignment is used in the sequencing process itself. The so-called shotgun sequencing technique (which was used, for example, by The Institute for Genomic Research to sequence the first bacterial genome, *Haemophilus influenzae*) does not produce entire chromosomes, but instead generates the sequences of many thousands of small DNA fragments (ranging from 35 to 900 nucleotides long, depending on the sequencing technology). The ends of these fragments overlap and, when aligned properly by a genome assembly program, can be used to reconstruct the complete genome. Shotgun sequencing yields sequence data quickly, but the task of assembling the fragments can be quite complicated for larger genomes. For a genome as large as the human genome, it may take many days of CPU time on large-memory, multiprocessor computers to assemble the fragments, and the resulting assembly will usually contain numerous gaps that have to be filled in later. Shotgun sequencing is the method of choice for virtually all genomes sequenced today, and genome assembly algorithms are a critical area of bioinformatics research.

Another aspect of bioinformatics in sequence analysis is annotation, which involves computational gene finding to search for protein-coding genes, RNA genes, and other functional sequences within a genome. Not all of the nucleotides within a genome are part of genes. Within the genome of higher organisms, large parts of the DNA do not serve any obvious purpose. This so-called junk DNA may, however, contain unrecognized functional elements. Bioinformatics helps to bridge the gap between genome and proteome projects--for example, in the use of DNA sequences for protein identification.

Genome annotation

In the context of genomics, **annotation** is the process of marking the genes and other biological features in a DNA sequence. The first genome annotation software system was designed in 1995 by Dr. Owen White, who was part of the team at The Institute for Genomic Research that sequenced and analyzed the first genome of a free-living organism to be decoded, the bacterium *Haemophilus influenzae*. Dr. White built a software system to find the genes (places in the DNA sequence that encode a protein), the transfer RNA, and other features, and to make initial assignments of function to those genes. Most current genome annotation systems work similarly, but the programs available for analysis of genomic DNA are constantly changing and improving.

Computational evolutionary biology

Evolutionary biology is the study of the origin and descent of species, as well as their change over time. Informatics has assisted evolutionary biologists in several key ways; it has enabled researchers to:

- trace the evolution of a large number of organisms by measuring changes in their DNA, rather than through physical taxonomy or physiological observations alone,
- more recently, compare entire genomes, which permits the study of more complex evolutionary events, such as gene duplication, horizontal gene transfer, and the prediction of factors important in bacterial speciation,
- build complex computational models of populations to predict the outcome of the system over time
- track and share information on an increasingly large number of species and organisms

Future work endeavours to reconstruct the now more complex tree of life.

The area of research within computer science that uses genetic algorithms is sometimes confused with computational evolutionary biology, but the two areas are not necessarily related.

Analysis of gene expression

The expression of many genes can be determined by measuring mRNA levels with multiple techniques including microarrays, expressed cDNA sequence tag (EST) sequencing, serial analysis of gene expression (SAGE) tag sequencing, massively parallel signature sequencing (MPSS), or various applications of multiplexed in-situ hybridization. All of these techniques are extremely noise-prone and/or subject to bias in the biological measurement, and a major research area in computational biology involves developing statistical tools to separate signal from noise in high-throughput gene expression studies. Such studies are often used to determine the genes implicated in a disorder: one might compare microarray data from cancerous epithelial cells to data from non-cancerous cells to determine the transcripts that are up-regulated and down-regulated in a particular population of cancer cells.

Analysis of regulation

Regulation is the complex orchestration of events starting with an extracellular signal such as a hormone and leading to an increase or decrease in the activity of one or more proteins. Bioinformatics techniques have been applied to explore various steps in this process. For example, promoter analysis involves the identification and study of sequence motifs in the DNA surrounding the coding region of a gene. These motifs influence the extent to which that region is transcribed into mRNA. Expression data can be used to infer gene regulation: one might compare microarray data from a wide variety of states of an organism to form hypotheses about the genes involved in each state. In a single-cell organism, one might compare stages of the cell cycle, along with various stress conditions (heat shock, starvation, etc.). One can then apply clustering algorithms to that expression data to determine which genes are co-expressed. For example, the upstream regions (promoters) of co-expressed genes can be searched for over-represented regulatory elements.

Analysis of protein expression

Protein microarrays and high throughput (HT) mass spectrometry (MS) can provide a snapshot of the proteins present in a biological sample. Bioinformatics is very much involved in making sense of protein microarray and HT MS data; the former approach faces similar problems as with microarrays targeted at mRNA, the latter involves the problem of matching large amounts of mass data against predicted masses from protein sequence databases, and the complicated statistical analysis of samples where multiple, but incomplete peptides from each protein are detected.

Analysis of mutations in cancer

In cancer, the genomes of affected cells are rearranged in complex or even unpredictable ways. Massive sequencing efforts are used to identify previously unknown point mutations in a variety of genes in cancer. Bioinformaticians continue to produce specialized automated systems to manage the sheer volume of sequence data produced, and they create new algorithms and software to compare the sequencing results to the growing collection of human genome sequences and germline polymorphisms. New physical detection technologies are employed, such as oligonucleotide microarrays to identify chromosomal gains and losses (called comparative genomic hybridization), and single-nucleotide polymorphism arrays to detect known *point mutations*. These detection methods simultaneously measure several hundred thousand sites throughout the genome, and when used in high-throughput to measure thousands of samples, generate terabytes of data per experiment. Again the massive amounts and new types of data generate new opportunities for bioinformaticians. The data is often found to contain considerable variability, or noise, and thus Hidden Markov model and change-point analysis methods are being developed to infer real copy number changes.

Another type of data that requires novel informatics development is the analysis of lesions found to be recurrent among many tumors .

Prediction of protein structure

Protein structure prediction is another important application of bioinformatics. The amino acid sequence of a protein, the so-called primary structure, can be easily determined from the sequence on the gene that codes for it. In the vast majority of cases, this primary structure uniquely determines a structure in its native environment. (Of course, there are exceptions, such as the bovine spongiform encephalopathy - aka Mad Cow Disease - prion.) Knowledge of this structure is vital in understanding the function of the protein. For lack of better terms, structural information is usually classified as one of *secondary*, *tertiary* and *quaternary* structure. A viable general solution to such predictions remains an open problem. As of now, most efforts have been directed towards heuristics that work most of the time.

One of the key ideas in bioinformatics is the notion of homology. In the genomic branch of bioinformatics, homology is used to predict the function of a gene: if the sequence of gene *A*, whose function is known, is homologous to the sequence of gene *B*, whose function is unknown, one could infer that *B* may share *A*'s function. In the structural branch of bioinformatics, homology is used to determine which parts of a protein are important in structure formation and interaction with other proteins. In a technique called homology modeling, this information is used to predict the structure of a protein once the structure of a homologous protein is known. This currently remains the only way to predict protein structures reliably.

One example of this is the similar protein homology between hemoglobin in humans and the hemoglobin in legumes (leghemoglobin). Both serve the same purpose of transporting oxygen in the organism. Though both of these proteins have completely different amino acid sequences, their protein structures are virtually identical, which reflects their near identical purposes.

Other techniques for predicting protein structure include protein threading and *de novo* (from scratch) physics-based modeling.

See also: structural motif and structural domain.

Comparative genomics

The core of comparative genome analysis is the establishment of the correspondence between genes (orthology analysis) or other genomic features in different organisms. It is these intergenomic maps that make it possible to trace the evolutionary processes responsible for the divergence of two genomes. A multitude of evolutionary events acting at various organizational levels shape genome evolution. At the lowest level, point mutations affect individual nucleotides. At a higher level, large chromosomal segments undergo duplication, lateral transfer, inversion, transposition, deletion and insertion. Ultimately, whole genomes are involved in processes of hybridization, polyploidization and endosymbiosis, often leading to rapid speciation. The complexity of genome evolution poses many exciting challenges to developers of mathematical models and algorithms, who have recourse to a spectra of algorithmic, statistical and mathematical techniques, ranging from exact, heuristics, fixed parameter and approximation algorithms for problems based on parsimony models to Markov Chain Monte Carlo algorithms for Bayesian analysis of problems based on probabilistic models.

Many of these studies are based on the homology detection and protein families computation.

Modeling biological systems

Systems biology involves the use of computer simulations of cellular subsystems (such as the networks of metabolites and enzymes which comprise metabolism, signal transduction pathways and gene regulatory networks) to both analyze and visualize the complex connections of these cellular processes. Artificial life or virtual evolution attempts to understand evolutionary processes via the computer simulation of simple (artificial) life forms.

High-throughput image analysis

Computational technologies are used to accelerate or fully automate the processing, quantification and analysis of large amounts of high-information-content biomedical imagery. Modern image analysis systems augment an observer's ability to make measurements from a large or complex set of images, by improving accuracy, objectivity, or speed. A fully developed analysis system may completely replace the observer. Although these systems are not unique to biomedical imagery, biomedical imaging is becoming more important for both diagnostics and research. Some examples are:

- high-throughput and high-fidelity quantification and sub-cellular localization (high-content screening, cytohistopathology, Bioimage informatics)
- morphometrics
- clinical image analysis and visualization
- determining the real-time air-flow patterns in breathing lungs of living animals
- quantifying occlusion size in real-time imagery from the development of and recovery during arterial injury
- making behavioral observations from extended video recordings of laboratory animals
- infrared measurements for metabolic activity determination
- inferring clone overlaps in DNA mapping, e.g. the Sulston score

Protein-protein docking

In the last two decades, tens of thousands of protein three-dimensional structures have been determined by X-ray crystallography and Protein nuclear magnetic resonance spectroscopy (protein NMR). One central question for the biological scientist is whether it is practical to predict possible protein-protein interactions only based on these 3D shapes, without doing protein-protein interaction experiments. A variety of methods have been developed to tackle the Protein-protein docking problem, though it seems that there is still much work to be done in this field.

Software and tools

Software tools for bioinformatics range from simple command-line tools, to more complex graphical programs and standalone web-services available from various bioinformatics companies or public institutions.

Web services in bioinformatics

SOAP and REST-based interfaces have been developed for a wide variety of bioinformatics applications allowing an application running on one computer in one part of the world to use algorithms, data and computing resources on servers in other parts of the world. The main advantages derive from the fact that end users do not have to deal with software and database maintenance overheads.

Basic bioinformatics services are classified by the EBI into three categories: SSS (Sequence Search Services), MSA (Multiple Sequence Alignment) and BSA (Biological Sequence Analysis). The availability of these service-oriented bioinformatics resources demonstrate the applicability of web based bioinformatics solutions, and range from a collection of standalone tools with a common data format under a single, standalone or web-based interface, to integrative, distributed and extensible bioinformatics workflow management systems.

See also

- Bioinformatics companies
- Health informatics
- Computational biomodeling
- Computational genomics
- DNA sequencing theory
- Dot plot (bioinformatics)
- Functional genomics
- Margaret Oakley Dayhoff
- Metabolic network modelling
- Molecular design software
- Molecular modeling on GPU
- Morphometrics
- Protein-protein interaction prediction
- List of scientific journals in bioinformatics
- Nucleic acid simulation software

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- Catalyzing Inquiry at the Interface of Computing and Biology (2005) CSTB report (<http://www.nap.edu/catalog/11480.html>)
- Calculating the Secrets of Life: Contributions of the Mathematical Sciences and computing to Molecular Biology (1995) (<http://www.nap.edu/catalog/2121.html>)
- Foundations of Computational and Systems Biology MIT Course (<http://ocw.mit.edu/OcwWeb/Biology/7-91JSpring2004/LectureNotes/index.htm>)
- Computational Biology: Genomes, Networks, Evolution Free MIT Course (<http://compbio.mit.edu/6.047/>)
- Algorithms for Computational Biology Free MIT Course (<http://ocw.mit.edu/OcwWeb/Electrical-Engineering-and-Computer-Science/6-096Spring-2005/CourseHome/index.htm>)
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External links

- Bioinformatics Organization (<http://bioinformatics.org/>)
 - Bioinformatics Research Groups (http://www.google.com/Top/Science/Biology/Bioinformatics/Research_Groups/) - Google Directory
 - EMBnet (<http://www.embnet.org/>)
 - Open Bioinformatics Foundation (<http://www.open-bio.org/>)
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Genomics

Genomics is a discipline in genetics concerning the study of the genomes of organisms. The field includes intensive efforts to determine the entire DNA sequence of organisms and fine-scale genetic mapping efforts. The field also includes studies of intragenomic phenomena such as heterosis, epistasis, pleiotropy and other interactions between loci and alleles within the genome. In contrast, the investigation of the roles and functions of single genes is a primary focus of molecular biology or genetics and is a common topic of modern medical and biological research. Research of single genes does not fall into the definition of genomics unless the aim of this genetic, pathway, and functional information analysis is to elucidate its effect on, place in, and response to the entire genome's networks.

For the United States Environmental Protection Agency, "the term "genomics" encompasses a broader scope of scientific inquiry associated technologies than when genomics was initially considered. A genome is the sum total of all an individual organism's genes. Thus, genomics is the study of all the genes of a cell, or tissue, at the DNA (genotype), mRNA (transcriptome), or protein (proteome) levels."^[1]

History

Genomics was established by Fred Sanger when he first sequenced the complete genomes of a virus and a mitochondrion. His group established techniques of sequencing, genome mapping, data storage, and bioinformatic analyses in the 1970-1980s. A major branch of genomics is still concerned with sequencing the genomes of various organisms, but the knowledge of full genomes has created the possibility for the field of functional genomics, mainly concerned with patterns of gene expression during various conditions. The most important tools here are microarrays and bioinformatics. Study of the full set of proteins in a cell type or tissue, and the changes during various conditions, is called proteomics. A related concept is materiomics, which is defined as the study of the material properties of biological materials (e.g. hierarchical protein structures and materials, mineralized biological tissues, etc.) and their effect on the macroscopic function and failure in their biological context, linking processes, structure and properties at multiple scales through a materials science approach. The actual term 'genomics' is thought to have been coined by Dr. Tom Roderick, a geneticist at the Jackson Laboratory (Bar Harbor, ME) over beer at a meeting held in Maryland on the mapping of the human genome in 1986.

In 1972, Walter Fiers and his team at the Laboratory of Molecular Biology of the University of Ghent (Ghent, Belgium) were the first to determine the sequence of a gene: the gene for Bacteriophage MS2 coat protein.^[2] In 1976, the team determined the complete nucleotide-sequence of bacteriophage MS2-RNA.^[3] The first DNA-based genome to be sequenced in its entirety was that of bacteriophage Φ -X174; (5,368 bp), sequenced by Frederick Sanger in 1977.^[4]

The first free-living organism to be sequenced was that of *Haemophilus influenzae* (1.8 Mb) in 1995, and since then genomes are being sequenced at a rapid pace.

As of September 2007, the complete sequence was known of about 1879 viruses ^[5], 577 bacterial species and roughly 23 eukaryote organisms, of which about half are fungi. ^[6] Most of the bacteria whose genomes have been completely sequenced are problematic disease-causing agents, such as *Haemophilus influenzae*. Of the other sequenced species, most were chosen because they were well-studied model organisms or promised to become good models. Yeast (*Saccharomyces cerevisiae*) has long been an important model organism for the eukaryotic cell, while the fruit fly *Drosophila melanogaster* has been a very important tool (notably in early pre-molecular genetics). The worm *Caenorhabditis elegans* is an often used simple model for multicellular organisms. The zebrafish *Brachydanio rerio* is used for many developmental studies on the molecular level and the flower *Arabidopsis thaliana* is a model organism for flowering plants. The Japanese pufferfish (*Takifugu rubripes*) and the spotted green pufferfish (*Tetraodon nigroviridis*) are interesting because of their small and compact genomes, containing very little non-coding DNA compared to most species. ^[7] ^[8] The mammals dog (*Canis familiaris*), ^[9] brown rat (*Rattus*

norvegicus), mouse (*Mus musculus*), and chimpanzee (*Pan troglodytes*) are all important model animals in medical research.

Human genomics

A rough draft of the human genome was completed by the Human Genome Project in early 2001, creating much fanfare. By 2007 the human sequence was declared "finished" (less than one error in 20,000 bases and all chromosomes assembled). Display of the results of the project required significant bioinformatics resources. The sequence of the human reference assembly can be explored using the UCSC Genome Browser.

Bacteriophage genomics

Bacteriophages have played and continue to play a key role in bacterial genetics and molecular biology. Historically, they were used to define gene structure and gene regulation. Also the first genome to be sequenced was a bacteriophage. However, bacteriophage research did not lead the genomics revolution, which is clearly dominated by bacterial genomics. Only very recently has the study of bacteriophage genomes become prominent, thereby enabling researchers to understand the mechanisms underlying phage evolution. Bacteriophage genome sequences can be obtained through direct sequencing of isolated bacteriophages, but can also be derived as part of microbial genomes. Analysis of bacterial genomes has shown that a substantial amount of microbial DNA consists of prophage sequences and prophage-like elements. A detailed database mining of these sequences offers insights into the role of prophages in shaping the bacterial genome.^[10]

Cyanobacteria genomics

At present there are 24 cyanobacteria for which a total genome sequence is available. 15 of these cyanobacteria come from the marine environment. These are six *Prochlorococcus* strains, seven marine *Synechococcus* strains, *Trichodesmium erythraeum* IMS101 and *Crocospaera watsonii* WH8501. Several studies have demonstrated how these sequences could be used very successfully to infer important ecological and physiological characteristics of marine cyanobacteria. However, there are many more genome projects currently in progress, amongst those there are further *Prochlorococcus* and marine *Synechococcus* isolates, *Acaryochloris* and *Prochloron*, the N₂-fixing filamentous cyanobacteria *Nodularia spumigena*, *Lyngbya aestuarii* and *Lyngbya majuscula*, as well as bacteriophages infecting marine cyanobacteria. Thus, the growing body of genome information can also be tapped in a more general way to address global problems by applying a comparative approach. Some new and exciting examples of progress in this field are the identification of genes for regulatory RNAs, insights into the evolutionary origin of photosynthesis, or estimation of the contribution of horizontal gene transfer to the genomes that have been analyzed.^[11]

See also

- Full Genome Sequencing
- Computational genomics
- Nitrogenomics
- Metagenomics
- Predictive Medicine
- Personal genomics
- Psychogenomics

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External links

- Genomics Directory (<http://www.genomicsdirectory.com>): A one-stop biotechnology resource center for bioentrepreneurs, scientists, and students
- Annual Review of Genomics and Human Genetics (<http://arjournals.annualreviews.org/loi/genom/>)
- BMC Genomics (<http://www.biomedcentral.com/bmcgenomics/>): A BMC journal on Genomics
- Genomics (<http://www.genomics.co.uk/companylist.php>): UK companies and laboratories* Genomics journal (http://www.elsevier.com/wps/find/journaldescription.cws_home/622838/description#description)
- Genomics and Quantitative Genetics (<http://www.knoblauchpublishing.com>): An international electronic, open access journal publishing, inter alia, genomics research.
- Genomics.org (<http://genomics.org>): An openfree wiki based Genomics portal
- NHGRI (<http://www.genome.gov/>): US government's genome institute
- Pharmacogenomics in Drug Discovery and Development (<http://www.springer.com/humana+press/pharmacology+and+toxicology/book/978-1-58829-887-4>), a book on pharmacogenomics, diseases, personalized medicine, and therapeutics
- Tishchenko P. D. Genomics: New Science in the New Cultural Situation (<http://www.zpu-journal.ru/en/articles/detail.php?ID=342>)
- Undergraduate program on Genomic Sciences (spanish) (<http://www.lcg.unam.mx/>): One of the first undergraduate programs in the world
- JCVI Comprehensive Microbial Resource (<http://cmr.jcvi.org/>)
- Pathema: A Clade Specific Bioinformatics Resource Center (<http://pathema.jcvi.org/>)
- KoreaGenome.org (<http://koreagenome.org>): The first Korean Genome published and the sequence is available freely.
- GenomicsNetwork (<http://genomicsnetwork.ac.uk>): Looks at the development and use of the science and technologies of genomics.
- Institute for Genome Sciences (http://www.igs.umaryland.edu/research_topics.php): Genomics research.
- Institute for Genome Sciences (http://www.igs.umaryland.edu/research_topics.php): Genomics research.

Computational genomics

Computational genomics refers to the use of computational analysis to decipher biology from genome sequences and related data^[1], including both DNA and RNA sequence as well as other "post-genomic" data (i.e. experimental data obtained with technologies that require the genome sequence, such as genomic DNA microarrays). As such, computational genomics may be regarded as a subset of bioinformatics, but with a focus on using whole genomes (rather than individual genes) to understand the principles of how the DNA of a species controls its biology at the molecular level and beyond. With the current abundance of massive biological datasets, computational studies have become one of the most important means to biological discovery.^[2]

History

The roots of computational genomics are shared with those of bioinformatics. During the 1960s, Margaret Dayhoff and others at the National Biomedical Research Foundation assembled databases of homologous protein sequences for evolutionary study.^[3] Their research developed a phylogenetic tree that determined the evolutionary changes that were required for a particular protein to change into another protein based on the underlying amino acid sequences. This led them to create a scoring matrix that assessed the likelihood of one protein being related to another.

Beginning in the 1980s, databases of genome sequences began to be recorded, but this presented new challenges in the form of searching and comparing the databases of gene information. Unlike text-searching algorithms that are used on websites such as google or Wikipedia, searching for sections of genetic similarity requires one to find strings that are not simply identical, but similar. This led to the development of the Needleman-Wunsch algorithm, which is a dynamic programming algorithm for comparing sets of amino acid sequences with each other by using scoring matrices derived from the earlier research by Dayhoff. Later, the BLAST algorithm was developed for performing fast, optimized searches of gene sequence databases. BLAST and its derivatives are probably the most widely-used algorithms for this purpose.^[4]

The emergence of the phrase "computational genomics" coincides with the availability of complete sequenced genomes in the mid-to-late 1990's. The first meeting of the Annual Conference on Computational Genomics was organized by scientists from The Institute for Genomic Research (TIGR) in 1998, providing a forum for this speciality and effectively distinguishing this area of science from the more general fields of Genomics or Computational Biology.^[5]^[6] The first use of this term in scientific literature, according to MEDLINE abstracts, was just one year earlier in Nucleic Acids Research.^[7] The final Computational Genomics conference was held in 2006, featuring a keynote talk by Nobel Laureate Barry Marshall, co-discoverer of the link between *Helicobacter pylori* and stomach ulcers. As of 2010, the leading conferences in the field include Intelligent Systems for Molecular Biology (ISMB), RECOMB, and the Cold Spring Harbor Laboratory and Sanger Institute's meetings titled "Biology of Genomes" and "Genome Informatics".

The development of computer-assisted mathematics (using products such as Mathematica or Matlab) has helped engineers, mathematicians and computer scientists to start operating in this domain, and a public collection of case studies and demonstrations is growing, ranging from whole genome comparisons to gene expression analysis.^[8] This has increased the introduction of different ideas, including concepts from systems and control, information theory, strings analysis and data mining. It is anticipated that computational approaches will become and remain a standard topic for research and teaching, while students fluent in both topics start being formed in the multiple courses created in the past few years.

Contributions of computational genomics research to biology

Contributions of computational genomics research to biology include ^[2] :

- discovering subtle patterns in genomic sequences
- proposing cellular signalling networks
- proposing mechanisms of genome evolution
- predict precise locations of all human genes using comparative genomics techniques with several mammalian and vertebrate species
- predict conserved genomic regions that are related to early embryonic development
- discover potential links between repeated sequence motifs and tissue-specific gene expression
- measure regions of genomes that have undergone unusually rapid evolution

See also

- Bioinformatics
- Biowiki
- Computational biology
- Genomics
- Microarray
- BLAST
- Computational epigenetics

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- [5] [backPid]=67&cHash=fd69079f5e The 7th Annual Conference on Computational Genomics (2004) (http://www.jcvi.org/cms/press/press-releases/full-text/archive/2004//article/computational-genomics-conference-to-attract-leading-scientists/?tx_ttnews)
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External links

- Harvard Extension School Biophysics 101, Genomics and Computational Biology, <http://www.courses.fas.harvard.edu/~bphys101/info/syllabus.html>
- University of Bristol course in Computational Genomics, <http://www.computational-genomics.net/>

Proteomics

Proteomics is the large-scale study of proteins, particularly their structures and functions.^{[1] [2]} Proteins are vital parts of living organisms, as they are the main components of the physiological metabolic pathways of cells. The term "proteomics" was first coined in 1997^[3] to make an analogy with genomics, the study of the genes. The word "proteome" is a blend of "**protein**" and "**genome**", and was coined by Marc Wilkins in 1994 while working on the concept as a PhD student.^{[4] [5]} The proteome is the entire complement of proteins,^[4] including the modifications made to a particular set of proteins, produced by an organism or system. This will vary with time and distinct requirements, or stresses, that a cell or organism undergoes.



Robotic preparation of MALDI mass spectrometry samples on a sample carrier.

Complexity of the problem

After genomics, proteomics is considered the next step in the study of biological systems. It is much more complicated than genomics mostly because while an organism's genome is more or less constant, the proteome differs from cell to cell and from time to time. This is because distinct genes are expressed in distinct cell types. This means that even the basic set of proteins which are produced in a cell needs to be determined.

In the past this was done by mRNA analysis, but this was found not to correlate with protein content.^{[6] [7]} It is now known that mRNA is not always translated into protein,^[8] and the amount of protein produced for a given amount of mRNA depends on the gene it is transcribed from and on the current physiological state of the cell. Proteomics confirms the presence of the protein and provides a direct measure of the quantity present.

Post-translational modifications

Not only does the translation from mRNA cause differences, many proteins are also subjected to a wide variety of chemical modifications after translation. A lot of these post-translational modifications are critical to the protein's function.

Phosphorylation

One such modification is phosphorylation, which happens to many enzymes and structural proteins in the process of cell signaling. The addition of a phosphate to particular amino acids—most commonly serine and threonine^[9] mediated by serine/threonine kinases, or more rarely tyrosine mediated by tyrosine kinases—causes a protein to become a target for binding or interacting with a distinct set of other proteins that recognize the phosphorylated domain.

Because protein phosphorylation is one of the most-studied protein modifications many "proteomic" efforts are geared to determining the set of phosphorylated proteins in a particular cell or tissue-type under particular circumstances. This alerts the scientist to the signaling pathways that may be active in that instance.

Ubiquitination

Ubiquitin is a small protein that can be affixed to certain protein substrates by enzymes called E3 ubiquitin ligases. Determining which proteins are poly-ubiquitinated can be helpful in understanding how protein pathways are regulated. This is therefore an additional legitimate "proteomic" study. Similarly, once it is determined what substrates are ubiquitinated by each ligase, determining the set of ligases expressed in a particular cell type will be helpful.

Additional modifications

Listing all the protein modifications that might be studied in a "Proteomics" project would require a discussion of most of biochemistry; therefore, a short list will serve here to illustrate the complexity of the problem. In addition to phosphorylation and ubiquitination, proteins can be subjected to (among others) methylation, acetylation, glycosylation, oxidation and nitrosylation. Some proteins undergo ALL of these modifications, often in time-dependent combinations, aptly illustrating the potential complexity one has to deal with when studying protein structure and function.

Distinct proteins are made under distinct settings

Even if one is studying a particular cell type, that cell may make different sets of proteins at different times, or under different conditions. Furthermore, as mentioned, any one protein can undergo a wide range of post-translational modifications.

Therefore a "proteomics" study can become quite complex very quickly, even if the object of the study is very restricted. In more ambitious settings, such as when a biomarker for a tumor is sought - when the proteomics scientist is obliged to study sera samples from multiple cancer patients - the amount of complexity that must be dealt with is as great as in any modern biological project.

Limitations to genomic study

Scientists are very interested in proteomics because it gives a much better understanding of an organism than genomics. First, the level of transcription of a gene gives only a rough estimate of its level of expression into a protein. An mRNA produced in abundance may be degraded rapidly or translated inefficiently, resulting in a small amount of protein. Second, as mentioned above many proteins experience post-translational modifications that profoundly affect their activities; for example some proteins are not active until they become phosphorylated. Methods such as phosphoproteomics and glycoproteomics are used to study post-translational modifications. Third, many transcripts give rise to more than one protein, through alternative splicing or alternative post-translational modifications. Fourth, many proteins form complexes with other proteins or RNA molecules, and only function in the presence of these other molecules. Finally, protein degradation rate plays an important role in protein content.^[10]

Methods of studying proteins

Determining proteins which are post-translationally modified

One way in which a particular protein can be studied is to develop an antibody which is specific to that modification. For example, there are antibodies which only recognize certain proteins when they are tyrosine-phosphorylated, known as phospho-specific antibodies; also, there are antibodies specific to other modifications. These can be used to determine the set of proteins that have undergone the modification of interest.

For sugar modifications, such as glycosylation of proteins, certain lectins have been discovered which bind sugars. These too can be used.

A more common way to determine post-translational modification of interest is to subject a complex mixture of proteins to electrophoresis in "two-dimensions", which simply means that the proteins are electrophoresed first in one direction, and then in another... this allows small differences in a protein to be visualized by separating a modified protein from its unmodified form. This methodology is known as "two-dimensional gel electrophoresis".

Recently, another approach has been developed called PROTOMAP which combines SDS-PAGE with shotgun proteomics to enable detection of changes in gel-migration such as those caused by proteolysis or post translational modification.

Determining the existence of proteins in complex mixtures

Classically, antibodies to particular proteins or to their modified forms have been used in biochemistry and cell biology studies. These are among the most common tools used by practicing biologists today.

For more quantitative determinations of protein amounts, techniques such as ELISAs can be used.

For proteomic study, more recent techniques such as matrix-assisted laser desorption/ionization (MALDI) have been employed for rapid determination of proteins in particular mixtures and increasingly electrospray ionization (ESI).

Establishing protein-protein interactions

Most proteins function in collaboration with other proteins, and one goal of proteomics is to identify which proteins interact. This is especially useful in determining potential partners in cell signaling cascades.

Several methods are available to probe protein-protein interactions. The traditional method is yeast two-hybrid analysis. New methods include protein microarrays, immunoaffinity chromatography followed by mass spectrometry, dual polarisation interferometry and experimental methods such as phage display and computational methods

Practical applications of proteomics

One of the most promising developments to come from the study of human genes and proteins has been the identification of potential new drugs for the treatment of disease. This relies on genome and proteome information to identify proteins associated with a disease, which computer software can then use as targets for new drugs. For example, if a certain protein is implicated in a disease, its 3D structure provides the information to design drugs to interfere with the action of the protein. A molecule that fits the active site of an enzyme, but cannot be released by the enzyme, will inactivate the enzyme. This is the basis of new drug-discovery tools, which aim to find new drugs to inactivate proteins involved in disease. As genetic differences among individuals are found, researchers expect to use these techniques to develop personalized drugs that are more effective for the individual.

A computer technique which attempts to fit millions of small molecules to the three-dimensional structure of a protein is called "virtual ligand screening". The computer rates the quality of the fit to various sites in the protein, with the goal of either enhancing or disabling the function of the protein, depending on its function in the cell. A

good example of this is the identification of new drugs to target and inactivate the HIV-1 protease. The HIV-1 protease is an enzyme that cleaves a very large HIV protein into smaller, functional proteins. The virus cannot survive without this enzyme; therefore, it is one of the most effective protein targets for killing HIV.

Biomarkers

The FDA defines a biomarker as, “A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention”.

Understanding the proteome, the structure and function of each protein and the complexities of protein-protein interactions will be critical for developing the most effective diagnostic techniques and disease treatments in the future.

An interesting use of proteomics is using specific protein biomarkers to diagnose disease. A number of techniques allow to test for proteins produced during a particular disease, which helps to diagnose the disease quickly. Techniques include western blot, immunohistochemical staining, enzyme linked immunosorbent assay (ELISA) or mass spectrometry.

Current research methodologies

There are many approaches to attempting to characterize the human proteome, which is estimated to exceed 100,000 unique forms, 25,000 genes plus post-translational modifications.

See also

- Proteomic chemistry
 - Bioinformatics
 - Cytomics
 - Genomics
 - List of omics topics in biology
 - Metabolomics
 - Lipidomics
 - Shotgun proteomics
 - Top-down proteomics
 - Bottom-up proteomics
 - Systems biology
 - Transcriptomics
 - Phosphoproteomics
 - PEGylation
 - Functional genomics
 - Activity based proteomics
-

Protein databases

- UniProt
- Protein Information Resource (PIR)
- Swiss-Prot
- Protein Data Bank (PDB)
- National Center for Biotechnology Information (NCBI)
- Human Protein Reference Database
- Proteomics Identifications Database (PRIDE)
- Proteopedia The collaborative, 3D encyclopedia of proteins and other molecules.

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External links

- Proteomics (http://www.dmoz.org//Science/Biology/Biochemistry_and_Molecular_Biology/Biomolecules/Proteins_and_Enzymes/Proteomics/) at the Open Directory Project

Interactomics

Interactomics is a discipline at the intersection of bioinformatics and biology that deals with studying both the interactions and the consequences of those interactions between and among proteins, and other molecules within a cell^[1]. The network of all such interactions is called the Interactome. Interactomics thus aims to compare such networks of interactions (i.e., interactomes) between and within species in order to find how the traits of such networks are either preserved or varied. From a mathematical, or mathematical biology viewpoint an interactome network is a graph or a category representing the most important interactions pertinent to the normal physiological functions of a cell or organism.

Interactomics is an example of "top-down" systems biology, which takes an overhead, as well as overall, view of a biosystem or organism. Large sets of genome-wide and proteomic data are collected, and correlations between different molecules are inferred. From the data new hypotheses are formulated about feedbacks between these molecules. These hypotheses can then be tested by new experiments^[2].

Through the study of the interaction of all of the molecules in a cell the field looks to gain a deeper understanding of genome function and evolution than just examining an individual genome in isolation^[1]. Interactomics goes beyond cellular proteomics in that it not only attempts to characterize the interaction between proteins, but between all molecules in the cell.

Methods of interactomics

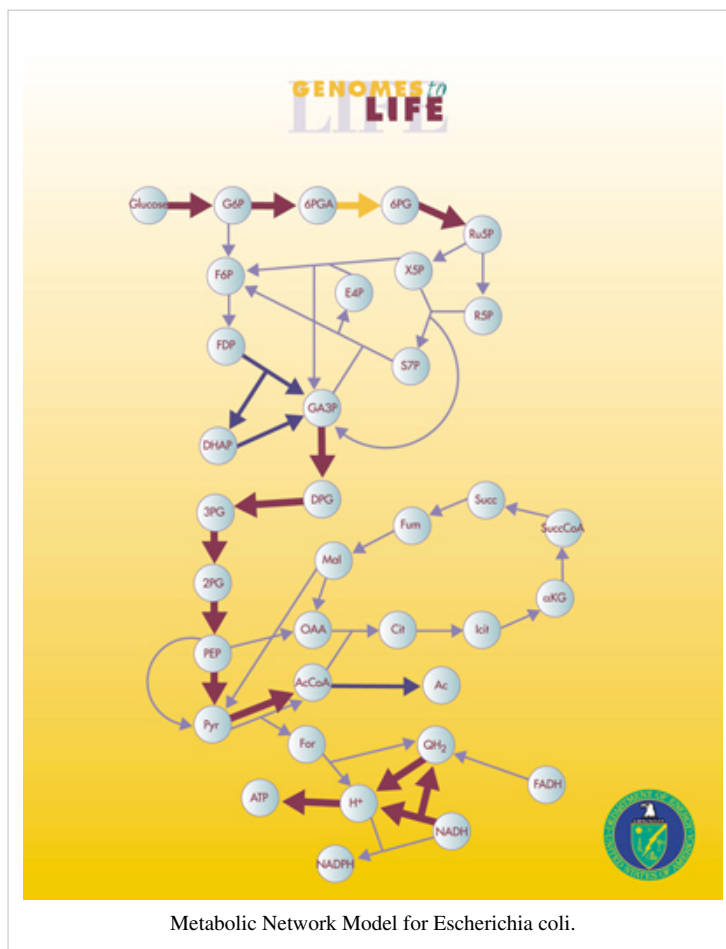
The study of the interactome requires the collection of large amounts of data by way of high throughput experiments. Through these experiments a large number of data points are collected from a single organism under a small number of perturbations^[2] These experiments include:

- Two-hybrid screening
 - Tandem Affinity Purification
 - X-ray tomography
 - Optical fluorescence microscopy
-

Recent developments

The field of interactomics is currently rapidly expanding and developing. While no biological interactomes have been fully characterized. Over 90% of proteins in *Saccharomyces cerevisiae* have been screened and their interactions characterized, making it the first interactome to be nearly fully specified^[3].

Also there have been recent systematic attempts to explore the human interactome^[1] and^[4].



Other species whose interactomes have been studied in some detail include *Caenorhabditis elegans* and *Drosophila melanogaster*.

Criticisms and concerns

Kiemer and Cesareni^[1] raise the following concerns with the current state of the field:

- The experimental procedures associated with the field are error prone leading to "noisy results". This leads to 30% of all reported interactions being artifacts. In fact, two groups using the same techniques on the same organism found less than 30% interactions in common.
- Techniques may be biased, i.e. the technique determines which interactions are found.
- Interactomes are not nearly complete with perhaps the exception of *S. cerevisiae*.
- While genomes are stable, interactomes may vary between tissues and developmental stages.
- Genomics compares amino acids, and nucleotides which are in a sense unchangeable, but interactomics compares proteins and other molecules which are subject to mutation and evolution.
- It is difficult to match evolutionarily related proteins in distantly related species.

See also

- Interaction network
- Proteomics
- Metabolic network
- Metabolic network modelling
- Metabolic pathway
- Genomics
- Mathematical biology
- Systems biology

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- [4] further citation needed

External links

- Interactomics.org (<http://interactomics.org>). A dedicated interactomics web site operated under BioLicense.
- Interactome.org (<http://interactome.org>). An interactome wiki site.
- PSIBase (<http://psibase.kobic.re.kr>) Structural Interactome Map of all Proteins.
- Omics.org (<http://omics.org>). An omics portal site that is openfree (under BioLicense)
- Genomics.org (<http://genomics.org>). A Genomics wiki site.
- Comparative Interactomics analysis of protein family interaction networks using PSIMAP (protein structural interactome map) (<http://bioinformatics.oxfordjournals.org/cgi/content/full/21/15/3234>)
- Interaction interfaces in proteins via the Voronoi diagram of atoms (http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6TYR-4KXVD30-2&_user=10&_coverDate=11/30/2006&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=8361bf3fe7834b4642cdda3b979de8bb)
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Biochemistry

Biochemistry is the study of chemical processes in living organisms. Biochemistry governs all living organisms and living processes. By controlling information flow through biochemical signalling and the flow of chemical energy through metabolism; biochemical processes give rise to the seemingly magical phenomenon of life. Much of biochemistry deals with the structures and functions of cellular components such as proteins, carbohydrates, lipids, nucleic acids and other biomolecules although increasingly processes rather than individual molecules are the main focus. Over the last 40 years biochemistry has become so successful at explaining living processes that now almost all areas of the life sciences from botany to medicine are engaged in biochemical research. Today the main focus of pure biochemistry is in understanding how biological molecules give rise to the processes that occur within living cells which in turn relates greatly to the study and understanding of whole organisms.

Among the vast number of different biomolecules, many are complex and large molecules (called *polymers*), which are composed of similar repeating subunits (called *monomers*). Each class of polymeric biomolecule has a different set of subunit types.^[1] For example, a protein is a polymer whose subunits are selected from a set of 20 or more amino acids. Biochemistry studies the chemical properties of important biological molecules, like proteins, and in particular the chemistry of enzyme-catalyzed reactions.

The biochemistry of cell metabolism and the endocrine system has been extensively described. Other areas of biochemistry include the genetic code (DNA, RNA), protein synthesis, cell membrane transport, and signal transduction.

History

Originally, it was generally believed that life was not subject to the laws of science the way non-life was. It was thought that only living beings could produce the molecules of life (from other, previously existing biomolecules). Then, in 1828, Friedrich Wöhler published a paper on the synthesis of urea, proving that organic compounds can be created artificially.^{[2] [3]}

The dawn of biochemistry may have been the discovery of the first enzyme, diastase (today called amylase), in 1833 by Anselme Payen. Eduard Buchner contributed the first demonstration of a complex biochemical process outside of a cell in 1896: alcoholic fermentation in cell extracts of yeast. Although the term “biochemistry” seems to have been first used in 1882, it is generally accepted that the formal coinage of biochemistry occurred in 1903 by Carl Neuberg, a German chemist. Previously, this area would have been referred to as physiological chemistry. Since then, biochemistry has advanced, especially since the mid-20th century, with the development of new techniques such as chromatography, X-ray diffraction, dual polarisation interferometry, NMR spectroscopy, radioisotopic labeling, electron microscopy and molecular dynamics simulations. These techniques allowed for the discovery and detailed analysis of many molecules and metabolic pathways of the cell, such as glycolysis and the Krebs cycle (citric acid cycle).

Another significant historic event in biochemistry is the discovery of the gene and its role in the transfer of information in the cell. This part of biochemistry is often called molecular biology. In the 1950s, James D. Watson, Francis Crick, Rosalind Franklin, and Maurice Wilkins were instrumental in solving DNA structure and suggesting its relationship with genetic transfer of information. In 1958, George Beadle and Edward Tatum received the Nobel Prize for work in fungi showing that one gene produces one enzyme. In 1988, Colin Pitchfork was the first person convicted of murder with DNA evidence, which led to growth of forensic science. More recently, Andrew Z. Fire and Craig C. Mello received the 2006 Nobel Prize for discovering the role of RNA interference (RNAi), in the silencing of gene expression

Today, there are three main types of biochemistry. Plant biochemistry involves the study of the biochemistry of autotrophic organisms such as photosynthesis and other plant specific biochemical processes. General biochemistry

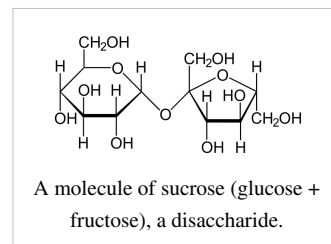
encompasses both plant and animal biochemistry. Human/medical/medicinal biochemistry focuses on the biochemistry of humans and medical illnesses.

Monomers and polymers

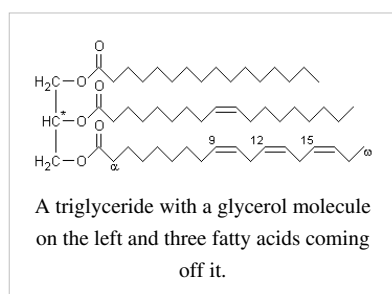
The four main classes of molecules in biochemistry are carbohydrates, lipids, proteins, and nucleic acids. Many biological molecules are polymers: in this terminology, **monomers** are relatively small micromolecules that are linked together to create large macromolecules, which are known as **polymers**. When monomers are linked together to synthesize a biological polymer, they undergo a process called dehydration synthesis.

Carbohydrates

Carbohydrates are made from monomers called *monosaccharides*. Some of these monosaccharides include glucose ($C_6H_{12}O_6$), fructose ($C_6H_{12}O_6$), and deoxyribose ($C_5H_{10}O_4$). When two monosaccharides undergo dehydration synthesis, water is produced, as two hydrogen atoms and one oxygen atom are lost from the two monosaccharides' hydroxyl group.



Lipids

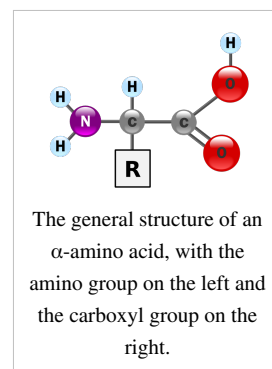


Lipids are usually made from one molecule of glycerol combined with other molecules. In triglycerides, the main group of bulk lipids, there is one molecule of glycerol and three fatty acids. Fatty acids are considered the monomer in that case, and may be saturated (no double bonds in the carbon chain) or unsaturated (one or more double bonds in the carbon chain).

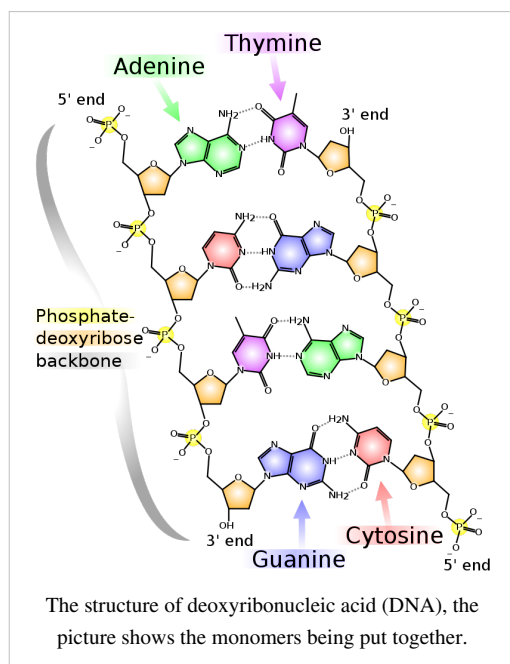
Lipids, especially phospholipids, are also used in various pharmaceutical products, either as co-solubilisers (e.g. in parenteral infusions) or else as drug carrier components (e.g. in a liposome or transfersome).

Proteins

Proteins are very large molecules – macro-biopolymers – made from monomers called *amino acids*. There are 20 standard amino acids, each containing a carboxyl group, an amino group, and a side chain (known as an "R" group). The "R" group is what makes each amino acid different, and the properties of the side chains greatly influence the overall three-dimensional conformation of a protein. When amino acids combine, they form a special bond called a peptide bond through dehydration synthesis, and become a **polypeptide**, or protein.



Nucleic acids



Nucleic acids are the molecules that make up DNA, an extremely important substance which all cellular organisms use to store their genetic information. The most common nucleic acids are deoxyribonucleic acid and ribonucleic acid. Their monomers are called nucleotides. The most common nucleotides are adenine, cytosine, guanine, thymine, and uracil. Adenine binds with thymine and uracil; thymine only binds with adenine; and cytosine and guanine can only bind with each other.

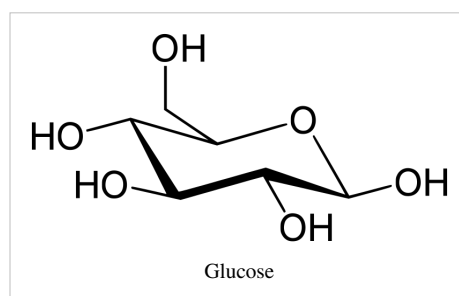
Carbohydrates

The function of carbohydrates includes energy storage and providing structure. Sugars are carbohydrates, but not all carbohydrates are sugars. There are more carbohydrates on Earth than any other known type of biomolecule; they are used to store energy and genetic information, as well as play important roles in cell to cell interactions and communications.

Monosaccharides

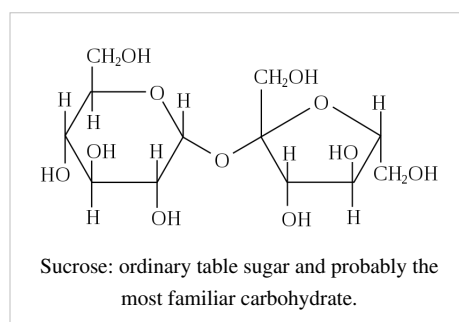
The simplest type of carbohydrate is a monosaccharide, which among other properties contains carbon, hydrogen, and oxygen, mostly in a ratio of 1:2:1 (generalized formula $C_n H_{2n} O_n$, where n is at least 3). Glucose, one of the most important carbohydrates, is an example of a monosaccharide. So is fructose, the sugar commonly associated with the sweet taste of fruits.^[4] [a] Some carbohydrates (especially after condensation to oligo- and polysaccharides) contain less carbon relative to H and O, which still are present in 2:1 (H:O) ratio.

Monosaccharides can be grouped into aldoses (having an aldehyde group at the end of the chain, e. g. glucose) and ketoses (having a keto group in their chain; e. g. fructose). Both aldoses and ketoses occur in an equilibrium (starting with chain lengths of C4) cyclic forms. These are generated by bond formation between one of the hydroxyl groups of the sugar chain with the carbon of the aldehyde or keto group to form a hemiacetal bond. This leads to saturated five-membered (in furanoses) or six-membered (in pyranoses) heterocyclic rings containing one O as heteroatom.



Disaccharides

Two monosaccharides can be joined together using dehydration synthesis, in which a hydrogen atom is removed from the end of one molecule and a hydroxyl group ($-OH$) is removed from the other; the remaining residues are then attached at the sites from which the atoms were removed. The $H-OH$ or H_2O is then released as a molecule of water, hence the term *dehydration*. The new molecule, consisting of two monosaccharides, is called a *disaccharide* and is conjoined together by a glycosidic or ether bond. The reverse reaction can also

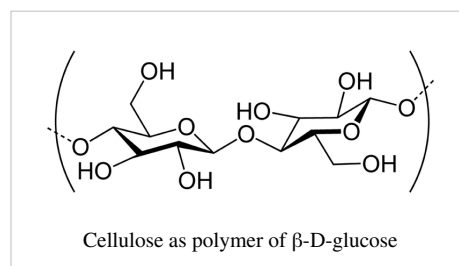


occur, using a molecule of water to split up a disaccharide and break the glycosidic bond; this is termed *hydrolysis*. The most well-known disaccharide is sucrose, ordinary sugar (in scientific contexts, called *table sugar* or *cane sugar* to differentiate it from other sugars). Sucrose consists of a glucose molecule and a fructose molecule joined together. Another important disaccharide is lactose, consisting of a glucose molecule and a galactose molecule. As most humans age, the production of lactase, the enzyme that hydrolyzes lactose back into glucose and galactose, typically decreases. This results in lactase deficiency, also called *lactose intolerance*.

Sugar polymers are characterised by having reducing or non-reducing ends. A reducing end of a carbohydrate is a carbon atom which can be in equilibrium with the open-chain aldehyde or keto form. If the joining of monomers takes place at such a carbon atom, the free hydroxy group of the pyranose or furanose form is exchanged with an OH-side chain of another sugar, yielding a full acetal. This prevents opening of the chain to the aldehyde or keto form and renders the modified residue non-reducing. Lactose contains a reducing end at its glucose moiety, whereas the galactose moiety form a full acetal with the C4-OH group of glucose. Saccharose does not have a reducing end because of full acetal formation between the aldehyde carbon of glucose (C1) and the keto carbon of fructose (C2).

Oligosaccharides and polysaccharides

When a few (around three to six) monosaccharides are joined together, it is called an *oligosaccharide* (*oligo-* meaning "few"). These molecules tend to be used as markers and signals, as well as having some other uses. Many monosaccharides joined together make a polysaccharide. They can be joined together in one long linear chain, or they may be branched. Two of the most common polysaccharides are cellulose and glycogen, both consisting of repeating glucose monomers.



- *Cellulose* is made by plants and is an important structural component of their cell walls. Humans can neither manufacture nor digest it.
- *Glycogen*, on the other hand, is an animal carbohydrate; humans and other animals use it as a form of energy storage.

Use of carbohydrates as an energy source

Glucose is the major energy source in most life forms. For instance, polysaccharides are broken down into their monomers (glycogen phosphorylase removes glucose residues from glycogen). Disaccharides like lactose or sucrose are cleaved into their two component monosaccharides.

Glycolysis (anaerobic)

Glucose is mainly metabolized by a very important ten-step pathway called glycolysis, the net result of which is to break down one molecule of glucose into two molecules of pyruvate; this also produces a net two molecules of ATP, the energy currency of cells, along with two reducing equivalents in the form of converting NAD^+ to NADH. This does not require oxygen; if no oxygen is available (or the cell cannot use oxygen), the NAD is restored by converting the pyruvate to lactate (lactic acid) (e. g. in humans) or to ethanol plus carbon dioxide (e. g. in yeast). Other monosaccharides like galactose and fructose can be converted into intermediates of the glycolytic pathway.

Aerobic

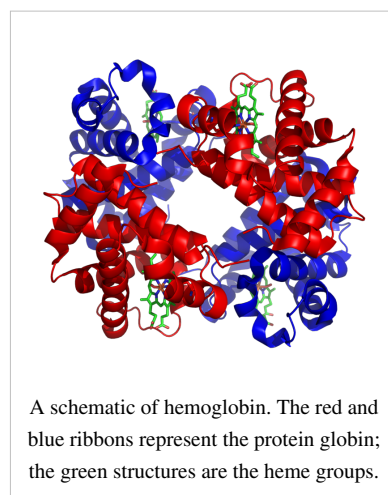
In aerobic cells with sufficient oxygen, like most human cells, the pyruvate is further metabolized. It is irreversibly converted to acetyl-CoA, giving off one carbon atom as the waste product carbon dioxide, generating another reducing equivalent as NADH. The two molecules acetyl-CoA (from one molecule of glucose) then enter the citric acid cycle, producing two more molecules of ATP, six more NADH molecules and two reduced (ubi)quinones (via FADH_2 as enzyme-bound cofactor), and releasing the remaining carbon atoms as carbon dioxide. The produced NADH and quinol molecules then feed into the enzyme complexes of the respiratory chain, an electron transport system transferring the electrons ultimately to oxygen and conserving the released energy in the form of a proton gradient over a membrane (inner mitochondrial membrane in eukaryotes). Thereby, oxygen is reduced to water and the original electron acceptors NAD^+ and quinone are regenerated. This is why humans breathe in oxygen and breathe out carbon dioxide. The energy released from transferring the electrons from high-energy states in NADH and quinol is conserved first as proton gradient and converted to ATP via ATP synthase. This generates an additional 28 molecules of ATP (24 from the 8 NADH + 4 from the 2 quinols), totaling to 32 molecules of ATP conserved per degraded glucose (two from glycolysis + two from the citrate cycle). It is clear that using oxygen to completely oxidize glucose provides an organism with far more energy than any oxygen-independent metabolic feature, and this is thought to be the reason why complex life appeared only after Earth's atmosphere accumulated large amounts of oxygen.

Gluconeogenesis

In vertebrates, vigorously contracting skeletal muscles (during weightlifting or sprinting, for example) do not receive enough oxygen to meet the energy demand, and so they shift to anaerobic metabolism, converting glucose to lactate. The liver regenerates the glucose, using a process called gluconeogenesis. This process is not quite the opposite of glycolysis, and actually requires three times the amount of energy gained from glycolysis (six molecules of ATP are used, compared to the two gained in glycolysis). Analogous to the above reactions, the glucose produced can then undergo glycolysis in tissues that need energy, be stored as glycogen (or starch in plants), or be converted to other monosaccharides or joined into di- or oligosaccharides. The combined pathways of glycolysis during exercise, lactate's crossing via the bloodstream to the liver, subsequent gluconeogenesis and release of glucose into the bloodstream is called the Cori cycle.

Proteins

Like carbohydrates, some proteins perform largely structural roles. For instance, movements of the proteins actin and myosin ultimately are responsible for the contraction of skeletal muscle. One property many proteins have is that they specifically bind to a certain molecule or class of molecules—they may be *extremely* selective in what they bind. Antibodies are an example of proteins that attach to one specific type of molecule. In fact, the enzyme-linked immunosorbent assay (ELISA), which uses antibodies, is currently one of the most sensitive tests modern medicine uses to detect various biomolecules. Probably the most important proteins, however, are the enzymes. These molecules recognize specific reactant molecules called *substrates*; they then catalyze the reaction between them. By lowering the activation energy, the enzyme speeds up that reaction by a rate of 10^{11} or more: a reaction that would normally take over 3,000 years to complete spontaneously might take less than a second with an enzyme. The enzyme itself is not used up in the process, and is free to catalyze the same reaction with a new set of substrates. Using various modifiers, the activity of the enzyme can be regulated, enabling control of the biochemistry of the cell as a whole.



In essence, proteins are chains of amino acids. An amino acid consists of a carbon atom bound to four groups. One is an amino group, —NH_2 , and one is a carboxylic acid group, —COOH (although these exist as —NH_3^+ and —COO^- under physiologic conditions). The third is a simple hydrogen atom. The fourth is commonly denoted " —R " and is different for each amino acid. There are twenty standard amino acids. Some of these have functions by themselves or in a modified form; for instance, glutamate functions as an important neurotransmitter.

Amino acids can be joined together via a peptide bond. In this dehydration synthesis, a water molecule is removed and the peptide bond connects the nitrogen of one amino acid's amino group to the carbon of the other's carboxylic acid group. The resulting molecule is called a *dipeptide*, and short stretches of amino acids (usually,

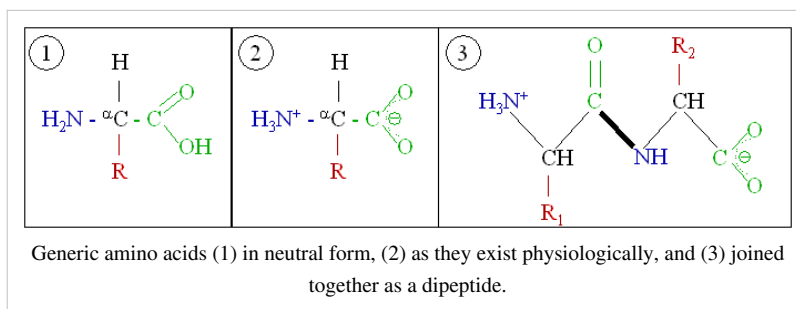
fewer than around thirty) are called *peptides* or *polypeptides*. Longer stretches merit the title *proteins*. As an example, the important blood serum protein albumin contains 585 amino acid residues.

The structure of proteins is traditionally described in a hierarchy of four levels. The primary structure of a protein simply consists of its linear sequence of amino acids; for instance, "alanine-glycine-tryptophan-serine-glutamate-asparagine-glycine-lysine-...". Secondary structure is concerned with local morphology (morphology being the study of structure). Some combinations of amino acids will tend to curl up in a coil called an α -helix or into a sheet called a β -sheet; some α -helices can be seen in the hemoglobin schematic above. Tertiary structure is the entire three-dimensional shape of the protein. This shape is determined by the sequence of amino acids. In fact, a single change can change the entire structure. The alpha chain of hemoglobin contains 146 amino acid residues; substitution of the glutamate residue at position 6 with a valine residue changes the behavior of hemoglobin so much that it results in sickle-cell disease. Finally quaternary structure is concerned with the structure of a protein with multiple peptide subunits, like hemoglobin with its four subunits. Not all proteins have more than one subunit.

Ingested proteins are usually broken up into single amino acids or dipeptides in the small intestine, and then absorbed. They can then be joined together to make new proteins. Intermediate products of glycolysis, the citric acid cycle, and the pentose phosphate pathway can be used to make all twenty amino acids, and most bacteria and plants possess all the necessary enzymes to synthesize them. Humans and other mammals, however, can only synthesize half of them. They cannot synthesize isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine. These are the essential amino acids, since it is essential to ingest them. Mammals do possess the enzymes to synthesize alanine, asparagine, aspartate, cysteine, glutamate, glutamine, glycine, proline, serine, and tyrosine, the nonessential amino acids. While they can synthesize arginine and histidine, they cannot produce it in sufficient amounts for young, growing animals, and so these are often considered essential amino acids.

If the amino group is removed from an amino acid, it leaves behind a carbon skeleton called an α -keto acid. Enzymes called transaminases can easily transfer the amino group from one amino acid (making it an α -keto acid) to another α -keto acid (making it an amino acid). This is important in the biosynthesis of amino acids, as for many of the pathways, intermediates from other biochemical pathways are converted to the α -keto acid skeleton, and then an amino group is added, often via transamination. The amino acids may then be linked together to make a protein.

A similar process is used to break down proteins. It is first hydrolyzed into its component amino acids. Free ammonia (NH_3), existing as the ammonium ion (NH_4^+) in blood, is toxic to life forms. A suitable method for excreting it must therefore exist. Different strategies have evolved in different animals, depending on the animals' needs. Unicellular organisms, of course, simply release the ammonia into the environment. Similarly, bony fish can release the ammonia into the water where it is quickly diluted. In general, mammals convert the ammonia into urea,



via the urea cycle.

Lipids

The term lipid comprises a diverse range of molecules and to some extent is a catchall for relatively water-insoluble or nonpolar compounds of biological origin, including waxes, fatty acids, fatty-acid derived phospholipids, sphingolipids, glycolipids and terpenoids (e.g. retinoids and steroids). Some lipids are linear aliphatic molecules, while others have ring structures. Some are aromatic, while others are not. Some are flexible, while others are rigid.

Most lipids have some polar character in addition to being largely nonpolar. Generally, the bulk of their structure is nonpolar or hydrophobic ("water-fearing"), meaning that it does not interact well with polar solvents like water. Another part of their structure is polar or hydrophilic ("water-loving") and will tend to associate with polar solvents like water. This makes them amphiphilic molecules (having both hydrophobic and hydrophilic portions). In the case of cholesterol, the polar group is a mere -OH (hydroxyl or alcohol). In the case of phospholipids, the polar groups are considerably larger and more polar, as described below.

Lipids are an integral part of our daily diet. Most oils and milk products that we use for cooking and eating like butter, cheese, ghee etc., are composed of fats. Vegetable oils are rich in various polyunsaturated fatty acids (PUFA). Lipid-containing foods undergo digestion within the body and are broken into fatty acids and glycerol, which are the final degradation products of fats and lipids.

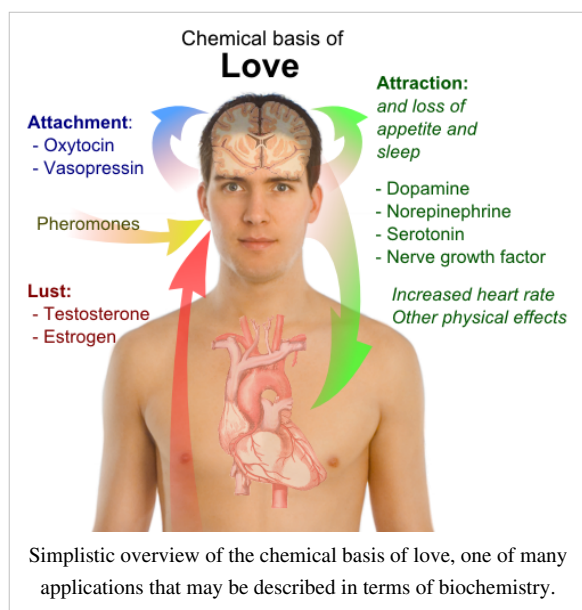
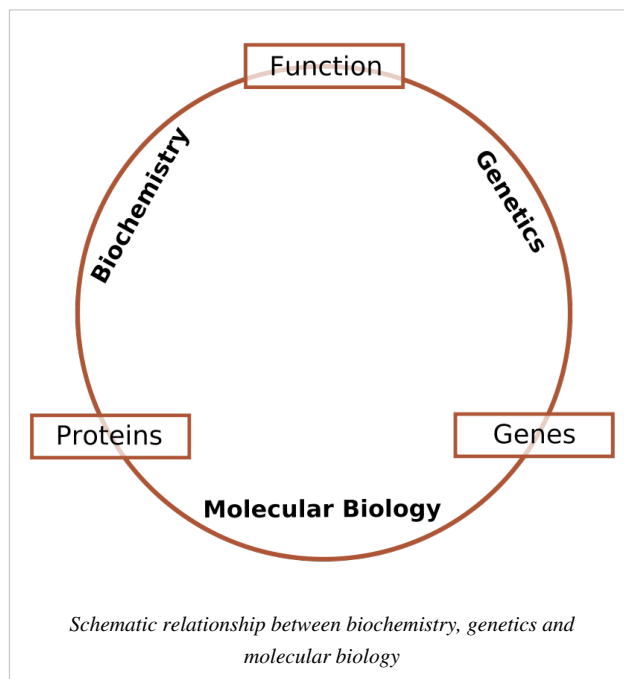
Nucleic acids

A nucleic acid is a complex, high-molecular-weight biochemical macromolecule composed of nucleotide chains that convey genetic information. The most common nucleic acids are deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Nucleic acids are found in all living cells and viruses. Aside from the genetic material of the cell, nucleic acids often play a role as second messengers, as well as forming the base molecule for adenosine triphosphate, the primary energy-carrier molecule found in all living organisms.

Nucleic acid, so called because of its prevalence in cellular nuclei, is the generic name of the family of biopolymers. The monomers are called nucleotides, and each consists of three components: a nitrogenous heterocyclic base (either a purine or a pyrimidine), a pentose sugar, and a phosphate group. Different nucleic acid types differ in the specific sugar found in their chain (e.g. DNA or deoxyribonucleic acid contains 2-deoxyribose). Also, the nitrogenous bases possible in the two nucleic acids are different: adenine, cytosine, and guanine occur in both RNA and DNA, while thymine occurs only in DNA and uracil occurs in RNA.

Relationship to other "molecular-scale" biological sciences

Researchers in biochemistry use specific techniques native to biochemistry, but increasingly combine these with techniques and ideas from genetics, molecular biology and biophysics. There has never been a hard-line between these disciplines in terms of content and technique. Today the terms *molecular biology* and *biochemistry* are nearly interchangeable. The following figure is a schematic that depicts one possible view of the relationship between the fields:



- **Biochemistry** is the study of the chemical substances and vital processes occurring in living organisms. Biochemists focus heavily on the role, function, and structure of biomolecules. The study of the chemistry behind biological processes and the synthesis of biologically active molecules are examples of biochemistry.
- **Genetics** is the study of the effect of genetic differences on organisms. Often this can be inferred by the absence of a normal component (e.g. one gene). The study of "mutants" – organisms which lack one or more functional components with respect to the so-called "wild type" or normal phenotype. Genetic interactions (epistasis) can often confound simple interpretations of such "knock-out" studies.
- **Molecular biology** is the study of molecular

underpinnings of the process of replication, transcription and translation of the genetic material. The central dogma of molecular biology where genetic material is transcribed into RNA and then translated into protein, despite being an oversimplified picture of molecular biology, still provides a good starting point for understanding the field. This picture, however, is undergoing revision in light of emerging novel roles for RNA.

- **Chemical Biology** seeks to develop new tools based on small molecules that allow minimal perturbation of biological systems while providing detailed information about their function. Further, chemical biology employs biological systems to create non-natural hybrids between biomolecules and synthetic devices (for example emptied viral capsids that can deliver gene therapy or drug molecules).

See also

Lists

- List of biochemistry topics
- List of biochemists
- List of biomolecules
- List of geneticists & biochemists
- List of nucleic acid simulation software
- Important publications in biochemistry (biology)
- Important publications in biochemistry (chemistry)

Related topics

- Biological psychiatry
- Biophysics
- Carbon chauvinism
- Chemical ecology
- Computational biomodeling
- EC number
- Hypothetical types of biochemistry
- International Union of Biochemistry and Molecular Biology
- Metabolome
- Metabolomics
- Molecular biology
- Molecular medicine
- Plant biochemistry
- Structural biology
- Stoichiometry
- Small molecule
- Veterinary

Notes

a. It should be noted that fructose is not the only sugar found in fruits. Glucose and sucrose are also found in varying quantities in various fruits, and indeed sometimes exceed the fructose present. For example, 32 % of the edible portion of date is glucose, compared with 23.70 % fructose and 8.20 % sucrose. Conversely, peaches contain more sucrose (6.66 %) than they do fructose (0.93 %) or glucose (1.47 %).^[5]

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External links

- The Virtual Library of Biochemistry and Cell Biology (<http://www.biochemweb.org/>)
- Biochemistry, 5th ed. (<http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowTOC&rid=stryer.TOC&depth=2>) Full text of Berg, Tymoczko, and Stryer, courtesy of NCBI.
- Biochemistry, 2nd ed. (<http://www.web.virginia.edu/Heidi/home.htm>) Full text of Garrett and Grisham.
- Biochemistry Animation (<http://www.1lec.com/Biochemistry/>) (Narrated Flash animations.)
- SystemsX.ch - The Swiss Initiative in Systems Biology (<http://www.systemsX.ch/>)
- Biochemistry Online Resources (<http://www.icademic.org/97445/Biochemistry/>) – Lists of Biochemistry departments, websites, journals, books and reviews, employment opportunities and events.

biochemical families: Carbohydrates (Glycosides, Alcohols) · Lipids (Steroids, Phospholipids, Glycolipids, Fatty acids, Tetrapyrroles) · Proteins (Amino acids, Peptides, Glycoproteins) · Nucleobases/Nucleic acids

Quantum biochemistry

Quantum chemistry is a branch of theoretical chemistry which applies quantum mechanics and quantum field theory to address problems in chemistry. One application of quantum chemistry is the electronic behavior of atoms and molecules relative to their chemical reactivity. Quantum chemistry lies on the border between chemistry and physics. Thus, significant contributions have been made by scientists from both fields. It has a strong and active overlap with the field of atomic physics and molecular physics, as well as physical chemistry.

Quantum chemistry mathematically describes the fundamental behavior of matter at the molecular scale^[1], but can span from elementary particles such as electrons (fermions) and photons (bosons) to the cosmos such as star-formation^[2]. It is, in principle, possible to describe all chemical systems using this theory. In practice, only the simplest chemical systems may realistically be investigated in purely quantum mechanical terms, and approximations must be made for most practical purposes (e.g., Hartree-Fock, post Hartree-Fock or Density functional theory, see computational chemistry for more details). Hence a detailed understanding of quantum mechanics is not necessary for most chemistry, as the important implications of the theory (principally the orbital approximation) can be understood and applied in simpler terms.

In quantum mechanics the Hamiltonian, or the physical state, of a particle can be expressed as the sum of two operators, one corresponding to kinetic energy and the other to potential energy. The Hamiltonian in the Schrödinger wave equation used in quantum chemistry does not contain terms for the spin of the electron.

Solutions of the Schrödinger equation for the hydrogen atom gives the form of the wave function for atomic orbitals, and the relative energy of the various orbitals. The orbital approximation can be used to understand the other atoms e.g. helium, lithium and carbon.

History

The history of quantum chemistry essentially began with the 1838 discovery of cathode rays by Michael Faraday, the 1859 statement of the black body radiation problem by Gustav Kirchhoff, the 1877 suggestion by Ludwig Boltzmann that the energy states of a physical system could be discrete, and the 1900 quantum hypothesis by Max Planck that any energy radiating atomic system can theoretically be divided into a number of discrete energy elements ϵ such that each of these energy elements is proportional to the frequency ν with which they each individually radiate

energy, as defined by the following formula:

$$\epsilon = h\nu$$

where h is a numerical value called Planck's Constant. Then, in 1905, to explain the photoelectric effect (1839), i.e., that shining light on certain materials can function to eject electrons from the material, Albert Einstein postulated, based on Planck's quantum hypothesis, that light itself consists of individual quantum particles, which later came to be called photons (1926). In the years to follow, this theoretical basis slowly began to be applied to chemical structure, reactivity, and bonding.

Electronic structure

The first step in solving a quantum chemical problem is usually solving the Schrödinger equation (or Dirac equation in relativistic quantum chemistry) with the electronic molecular Hamiltonian. This is called determining the **electronic structure** of the molecule. It can be said that the electronic structure of a molecule or crystal implies essentially its chemical properties. An exact solution for the Schrödinger equation can only be obtained for the hydrogen atom. Since all other atomic, or molecular systems, involve the motions of three or more "particles", their Schrödinger equations cannot be solved exactly and so approximate solutions must be sought.

Wave model

The foundation of quantum mechanics and quantum chemistry is the **wave model**, in which the atom is a small, dense, positively charged nucleus surrounded by electrons. Unlike the earlier Bohr model of the atom, however, the wave model describes electrons as "clouds" moving in orbitals, and their positions are represented by probability distributions rather than discrete points. The strength of this model lies in its predictive power. Specifically, it predicts the pattern of chemically similar elements found in the periodic table. The wave model is so named because electrons exhibit properties (such as interference) traditionally associated with waves. See wave-particle duality.

Valence bond

Although the mathematical basis of quantum chemistry had been laid by Schrödinger in 1926, it is generally accepted that the first true calculation in quantum chemistry was that of the German physicists Walter Heitler and Fritz London on the hydrogen (H_2) molecule in 1927. Heitler and London's method was extended by the American theoretical physicist John C. Slater and the American theoretical chemist Linus Pauling to become the **Valence-Bond (VB)** [or **Heitler-London-Slater-Pauling (HLSP)**] method. In this method, attention is primarily devoted to the pairwise interactions between atoms, and this method therefore correlates closely with classical chemists' drawings of bonds.

Molecular orbital

An alternative approach was developed in 1929 by Friedrich Hund and Robert S. Mulliken, in which electrons are described by mathematical functions delocalized over an entire molecule. The **Hund-Mulliken** approach or **molecular orbital (MO) method** is less intuitive to chemists, but has turned out capable of predicting spectroscopic properties better than the VB method. This approach is the conceptional basis of the **Hartree-Fock method** and further post Hartree-Fock methods.

Density functional theory

The **Thomas-Fermi model** was developed independently by Thomas and Fermi in 1927. This was the first attempt to describe many-electron systems on the basis of electronic density instead of wave functions, although it was not very successful in the treatment of entire molecules. The method did provide the basis for what is now known as **density functional theory**. Though this method is less developed than post Hartree-Fock methods, its significantly lower computational requirements (scaling typically no worse than n^3 with respect to n basis functions) allow it to tackle larger polyatomic molecules and even macromolecules. This computational affordability and often comparable accuracy to MP2 and CCSD (post-Hartree-Fock methods) has made it one of the most popular methods in computational chemistry at present.

Chemical dynamics

A further step can consist of solving the Schrödinger equation with the total molecular Hamiltonian in order to study the motion of molecules. Direct solution of the Schrödinger equation is called *quantum molecular dynamics*, within the semiclassical approximation *semiclassical molecular dynamics*, and within the classical mechanics framework *molecular dynamics (MD)*. Statistical approaches, using for example Monte Carlo methods, are also possible.

Adiabatic chemical dynamics

In **adiabatic dynamics**, interatomic interactions are represented by single scalar potentials called potential energy surfaces. This is the Born-Oppenheimer approximation introduced by Born and Oppenheimer in 1927. Pioneering applications of this in chemistry were performed by Rice and Ramsperger in 1927 and Kassel in 1928, and generalized into the RRKM theory in 1952 by Marcus who took the transition state theory developed by Eyring in 1935 into account. These methods enable simple estimates of unimolecular reaction rates from a few characteristics of the potential surface.

Non-adiabatic chemical dynamics

Non-adiabatic dynamics consists of taking the interaction between several coupled potential energy surface (corresponding to different electronic quantum states of the molecule). The coupling terms are called **vibronic couplings**. The pioneering work in this field was done by Stueckelberg, Landau, and Zener in the 1930s, in their work on what is now known as the Landau-Zener transition. Their formula allows the transition probability between two diabatic potential curves in the neighborhood of an avoided crossing to be calculated.

Quantum chemistry and quantum field theory

The application of quantum field theory (QFT) to chemical systems and theories has become increasingly common in the modern physical sciences. One of the first and most fundamentally explicit appearances of this is seen in the theory of the photomagnetron. In this system, plasmas, which are ubiquitous in both physics and chemistry, are studied in order to determine the basic quantization of the underlying bosonic field. However, quantum field theory is of interest in many fields of chemistry, including: nuclear chemistry, astrochemistry, sonochemistry, and quantum hydrodynamics. Field theoretic methods have also been critical in developing the ab initio Effective Hamiltonian theory of semi-empirical pi-electron methods.

See also

- Atomic physics
- Computational chemistry
- Condensed matter physics
- International Academy of Quantum Molecular Science
- Molecular modelling
- Physical chemistry
- Quantum chemistry computer programs
- Quantum electrochemistry
- QMC@Home
- Theoretical physics

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- ChemViz Curriculum Support Resources (<http://www.shodor.org/chemviz/>)
- Early ideas in the history of quantum chemistry (<http://www.quantum-chemistry-history.com/>)
- The Particle Adventure (<http://particleadventure.org/>)

Nobel lectures by quantum chemists

- Walter Kohn's Nobel lecture (<http://nobelprize.org/chemistry/laureates/1998/kohn-lecture.html>)
 - Rudolph Marcus' Nobel lecture (<http://nobelprize.org/chemistry/laureates/1992/marcus-lecture.html>)
 - Robert Mulliken's Nobel lecture (<http://nobelprize.org/chemistry/laureates/1966/mulliken-lecture.html>)
 - Linus Pauling's Nobel lecture (<http://nobelprize.org/chemistry/laureates/1954/pauling-lecture.html>)
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